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Dengue in India: Matters of the Heart

Milind Y Nadkar¹, Wasim Khot²

Dengue is an arthropod borne infection caused by RNA virus of the Flaviridae family. The pooled estimate of dengue seroprevalence in the Indian population and case fatality rate among laboratory confirmed dengue patients are 56.9% and 2.6% respectively.¹ Infection with dengue virus is asymptomatic in majority of the cases. Symptomatic dengue infection may be in the form of mild, moderate or severe dengue. Expanded dengue syndrome is an entity added to incorporate a wide spectrum of unusual manifestations of dengue infection affecting various organ systems including the heart.²

Cardiac involvement in dengue was thought to be a rare occurrence. Studies about cardiovascular manifestations of dengue have been published as early as 1973 when what was referred as “arboviral heart disease” was described from USA.³ From the Indian subcontinent cases of dengue myocarditis and pericarditis were reported from Srilanka around the same time.⁴

Cardiac manifestation in dengue fever ranges from asymptomatic bradycardia, heart blocks, tachyarrhythmias to severe myocarditis and pericardial effusion. The pathogenic mechanisms underlying this is not clear. Direct viral invasion, immune mechanisms, electrolyte imbalance, derangement of intracellular calcium ion storage, lactic acidosis, and ischemia due to hypotension all play a role.³ Striated muscle is the target of dengue infection. Alterations in calcium homeostasis is associated with myocardial dysfunction.⁶ The interaction between the NS1 and the glyocalyx layer of the vascular endothelium is thought to increase capillary permeability. The resulting plasma leakage can contribute to the cardiac dysfunction in the form of reduced preload, altered coronary microcirculation, and myocardial interstitial oedema. Fulminant dengue myocarditis is postulated to involve host genetics or increased viral cardiotropic allowing widespread myocyte damage.⁷

Classic myocarditis refers to inflammation of the heart muscle occurring as a result of exposure to either discrete external antigens such as viruses or internal triggers. The signs of myocarditis can vary from a subclinical rise in cardiac biomarkers or detection of asymptomatic electrocardiogram (ECG) abnormalities, through to the more severe clinical manifestations of dyspnoea, chest pain, palpitation, syncope and sudden death.⁸

ECG alterations in dengue are mostly transient and nonspecific, including sinus bradycardia, atrioventricular block, T wave, and ST-segment abnormalities. These were thought to occur mainly in recovery phase but ECG abnormalities are now known to occur during any phase of the disease. These arrhythmias tend to be self-limiting and benign, and might be the only sign of cardiac involvement, with normal biomarker levels and echocardiograms often documented.⁹ In the SriLankan outbreak of 2005, high proportion of patients (62%) admitted with dengue had ECG abnormalities, predominantly bradyarrhythmias, and T wave and ST-segment changes. These patients were more likely to develop hypotension than those with a normal ECG.¹⁰ Bradyarrhythmia, the commonest arrhythmia is significant when it occurs in the critical phase as hypovolaemia is also coexisting. Inability to mount an appropriate heart rate response to maintain cardiac output adds to haemodynamic instability.⁷ Cardiac biomarkers (troponin I and pro-B-type natriuretic peptide) have been found to be elevated. Echocardiography may show depressed LVEF. An Indian study of children hospitalized with dengue demonstrated evidence of left ventricular systolic dysfunction in 17%.¹¹ Patients with LV dysfunction required more fluids and had more complications of fluid overload than those without. As LVEF is preload dependent, whether this dysfunction reflected intravascular hypovolaemia, is unknown.¹² Endomyocardial biopsy is confirmatory. Myocardial involvement can also be confirmed using cardiac MRI findings including a hyperintense signal on T2-weighted images, as well as early and late gadolinium enhancement.¹³ Pericardial involvement is less common.

Management of cardiac involvement in dengue is mainly supportive. Cautious fluid resuscitation, aiming to give enough intravenous fluid therapy to maintain adequate tissue perfusion during the critical period of capillary leakage. No cardiac-specific treatments for dengue myocarditis exist. Standard treatment for cardiac failure with β-blockers, angiotensin-converting-enzyme inhibitors, and diuretics has been used successfully in these patients.⁷

A prospective observational study published in this issue was conducted at a tertiary centre in Kolkata to study the incidence of different cardiac manifestations of dengue fever from Jan 2016 to Dec 2017. These patients were followed up for a period of 6 months to 2 years. The incidence of cardiovascular involvement in this study was 12.5%. Bradycarrhythmias were commonest cardiac manifestations. Out of eight patients (6.6%) having bradyarrhythmias, four had sinus bradycardia. Three patients had junctional bradycardia. Orciprenalin was used in severe bradycardia. Single patient had 2:1 AV block requiring temporary pacemaker and recovered in two weeks. Others had complete recovery within a week. Four patients (3.3%) had left ventricular systolic dysfunction with global hypokinesia and recovered.

¹Professor and Head, ²Assistant Professor, Department of Medicine, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra
within 3 months. None of them had abnormal cardiac biomarkers which was unlike other studies. Moderate pericardial effusion was observed in two patients (1.6%) which resolved within 3 weeks. One patient had atrial fibrillation requiring pharmacologic cardioversion with amiodarone. In this study cardiac MRI or endomyocardial biopsy should be considered as confirmatory for myocardial involvement were not done in any patient. The authors could not find any association between severity of dengue fever and cardiac manifestations. The overall incidence of cardiac involvement was similar to other recent studies. In a large study of 1782 patients by Yingling Li et al during the 2014 outbreak in China the prevalence of myocarditis was 11.28%. Myocarditis increased with severity of Dengue. Shock was also increased significantly. In a study previously published in this journal, the incidence of myocarditis was 37.5%, bradycardia being the most common finding. Rhythm disturbance was noted in 5% of the patients with AV block being the most common (66.67%). In a recently published study by Papalkar et al also bradycardia was commonest arrhythmia seen in 9 (15%) patients, followed by sinus tachycardia in 6 (10%) and ST-T changes in 5 (8.33%), systolic dysfunction in 4 (6.67%) patients, and pericardial effusion was found in 2 (3.33%) patients. Eight (13.33%) patients had elevated CKMB levels.

Thus cardiac involvement is an important and neglected complication of dengue infection and a part of expanded dengue syndrome. The spectrum of cardiovascular manifestations in dengue is broad. Electrocardiogram should be done in patients of dengue fever with inappropriate bradycardia or tachycardia for clinical setting or age, cardiac specific symptoms, high-risk groups such as elderly and those with underlying heart disease. If abnormal these patients should undergo cardiac enzymes estimation and echocardiographic imaging. Echocardiography should also be considered in patients with shock unresponsive to adequate fluid therapy. As the management is mainly supportive early diagnosis is key.

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A Study on Cardiac Manifestations of Dengue Fever

Goutam Datta¹*, Pratik Mitra²

Abstract

Aims: Incidence of cardiac involvement in dengue fever varies between 15 –50%. Cardiac manifestations of dengue fever include asymptomatic sinus bradycardia, transient AV blocks, transient ventricular arrhythmias, myocarditis and pericardial effusion. This study was done with the objective of finding actual incidence of different cardiac manifestations of dengue fever in our tertiary care hospital.

Methods: One hundred and twenty dengue patients were studied between January 2016 to December 2017. Routine biochemical parameters like complete haemogram, liver function tests, renal function tests, electrolytes were checked in all cases. ECG, echocardiography, Troponin T were evaluated in every patients and they were corroborated with clinical features like chest pain, dyspnoea, palpitation. Patients with electrolyte abnormalities, preexisting heart disease, drugs interfering with heart rhythm were excluded from study.

Results: Fifteen patients had cardiac involvement (12.5%). Eight patient had bradyarhythmias (6.6%). Asymptomatic sinus bradycardia was commonest (3.3%). All had normal recovery within two weeks. Four patients had left ventricular systolic dysfunction (ejection fraction 35% - 45%) and there was spontaneous recovery within three months. Two patients had pericardial effusion which resolved within two weeks. Transient 2.1 AV block and atrial fibrillation were observed in two cases.

Conclusion: Cardiac manifestations of Dengue were present in 11.4 % of our patients. Brady arrhythmias (6.6%) were commonest manifestation which resolves spontaneously within seven to fourteen days. Left ventricular systolic dysfunction was present in 3.3% of patients which recovered within three months. Pericardial effusion was seen in 2.5% of patients. There were no significant tachyarhythmias in our patients except one case of atrial fibrillation.

Introduction

Dengue is a self-limited systemic viral infection caused by Flavi virus and is being transmitted between people by the mosquitoes Aedes aegypti and Aedes albopictus. There are four serotypes of dengue viruses - DEN 1, DEN 2, DEN 3 and DEN 4.¹ Dengue fever (DF) may have wide spectrum of presentations ranging from uncomplicated self-limiting febrile illness to severe dengue including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). According to The World Health Organization (WHO) data, 50 to 100 million infections occur yearly, including 500,000 dengue haemorrhagic fever (DHF) cases and 22,000 deaths, mostly among children.² Cardiac involvement in dengue has been poorly investigated and is uncommon. Cardiac manifestations of dengue fever include asymptomatic sinus bradycardia, transient AV blocks, transient ventricular arrhythmias, myocarditis and pericardial effusion. This study was done with the objective of finding actual incidence of different cardiac manifestations of dengue fever.

Materials and Methods

This prospective observational study was conducted at Department of Medicine and cardiology at EEDF hospital (Tertiary centre) in Calcutta. All consecutives dengue fever patients admitted between January 2016 to December 2017 were included in the study. Dengue cases were diagnosed according to the World Health Organization (WHO) 2009 criteria i.e. rapid test detection of nonstructural protein 1 (NS1) and/or immunoglobulin M (IgM) antibody on patients’ serum. One hundred and twenty patients were studied for two years. Minimum follow up period was six months and maximum two years. Informed consents were taken from all patients or their legal guardians and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki with prior approval by institution’s human research committee. Routine biochemical parameters like complete haemogram, liver function tests, renal function tests, electrolytes were checked in all cases. Electrocardiogram was done in all cases for three consecutive days. If ECG is abnormal, daily monitoring was continued.

Echocardiogram and Troponin T were checked in all patients. Clinical features like chest pain, dyspnea, palpitation, abnormalities in heart rate and rhythm were analyzed clinically and corroborated with the above investigations. Quantitative variables are reported as mean and the categorical variables as frequency or percentage.

Objectives of the Study

To study the incidence of different cardiac manifestations of dengue fever in our hospital.

Inclusion Criteria

a. Age ≥ 12 years
b. Fulfilling the WHO criteria for dengue
   c. Confirmed dengue serology

¹Associate Professor, Burdwan Medical College, West Bengal; ²Senior Consultant, EEDF Hospital, Kolkata, West Bengal; ³Corresponding Author

Received: 11.05.2018; Accepted: 20.12.2018
Exclusion criteria

a. Patients with medications which can affect heart rate.
b. Patients with preexisting heart disease.
c. Patients with electrolyte abnormalities.

Results

The mean age of our study group was 32 years. The youngest patient was 13 years old and the oldest patient was 74 years old (Table 1). There were 74 males (61%) and 46 (38%) females in our study. Fifteen patients had cardiac complications. Incidence was 12.5%. Bradycardias were most common cardiac manifestations in our study. There were eight patients (6.6%) having different types of bradycardias (Figure 1). Four patients had sinus bradycardia with varying heart rate between 40 to 50 beats/minute. Heart rate of 50 or less was taken as inclusion criteria. All of them had recovery within seven days. Those who had heart rate of 45 or less were put on orciprenaline. Criteria for putting temporary pacemaker was heart rate of less than forty. Three patents had junctional bradycardia with heart rate ranging from forty to forty five beats per minute. All of them were on orciprenaline and their heart rate came back to normal within seven days. Only one patient had 2:1 AV nodal block and he had a heart rate of 35 to 38 beats/minute. He was only 16 years old and took almost two weeks to recover. He was on temporary pacemaker for two weeks. Occasional ventricular ectopics were seen in few patients but they were not clinically significant.

Patients who had experienced bradycardias were in the age group of sixteen to forty. Left ventricular systolic function was assessed in every patient by echocardiography. Four patients (3.3%) had left ventricular systolic dysfunction. Regional wall motion abnormalities were absent but there were global hypokinesia. All of them were having mid-range left ventricular systolic dysfunction (ejection fraction 35% to 45%) (Figure 2). Two them presented with left ventricular failure and they responded to medical therapy. Left ventricular systolic dysfunction recovered within three months. But troponin T was not elevated in none of the patients. Two patients were in age group of twenty to thirty and two were in thirty to forty years age group. Pericardial effusion was observed in two patients (1.6%). Both of them were having moderate pericardial effusion. None of the cases progressed to massive pericardial effusion or tamponade. Echocardiogram was done serially and pericardial effusion resolved within three weeks. There was no associated pleural effusion, left ventricular dysfunction or pneumonia. They were in twenty to thirty years age group. None of the patients had thrombocytopenia, deranged liver or renal function tests. Only one patient had atrial fibrillation and she was seventy years old. Pharmacological cardioversion was done by amiodarone infusion.

Discussion

Dengue like many viral infections can cause myocardial injury, either by direct invasion or by autoimmune reaction resulting in myocardial inflammation. Direct invasion incites different cytokines and can release inflammatory mediators like TNF-alpha, interleukins, oxygen free radicals. Dengue virus and antigen may associate with myocardial receptor site and can trigger cell mediated immune response causing myocardial injury, which recovers with resolution of infection. The cardiac abnormalities in dengue are transient and self-limited. It could be attributed to subclinical viral myocarditis. Cardiac manifestation in dengue fever ranges from asymptomatic bradycardia to severe myocarditis. Cardiac rhythm abnormalities such as sinus bradycardia, junctional bradycardia, first degree AV block, transient AV block, transient ventricular arrhythmias have been observed in different studies during acute or convalescence phase of dengue infection. Transient myocarditis, systolic and diastolic dysfunction and pericardial effusion have also been reported during acute phase of infection.

In the study by Thein, Leo et al, minimum pulse rate was 34/minute and the maximum pulse rate was 140/minute. In the study by Latheef et al mean heart rates were significantly lower in the dengue group 87.6 beats/min (dengue) compared to the control group. In our study minimum pulse rate was thirty five per minute and patient was suffering from 2:1 AV nodal block. Rest of the patients with rhythm abnormalities had heart rate of forty to forty five beats per minute. Those patients who had acute lung injury or dengue shock syndrome in our study had sinus tachycardia with heart rate in the range of 120-140/minutes (Figure 3). Other patients did not have tachycardia. Asymptomatic sinus bradycardia was most common rhythm

Table 1: Distribution of age group, dengue cases and cardiac abnormalities

<table>
<thead>
<tr>
<th>Age group in years</th>
<th>13-20</th>
<th>21-30</th>
<th>31-40</th>
<th>41-50</th>
<th>51-60</th>
<th>61-70</th>
<th>71-80</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of Dengue fever</td>
<td>36</td>
<td>24</td>
<td>22</td>
<td>16</td>
<td>10</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Junctional bradycardia</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AV nodal block</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
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<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Pericardial effusion</td>
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<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Fig. 1: Incidence of cardiac manifestations in Dengue fever

Fig. 2: Different cardiac manifestations of Dengue fever
abnormalities in our study (3.3%). Junctional bradycardia was observed in three patients (2.5%). In the study by Gupta et al., sinus bradycardia was found in 14.28%, and sinus tachycardia 21.4%. AV dissociation with sinus node dysfunction was observed in one patient, which resolved in 24 hours. Kaushik et al have described ativoventricular dissociation and sino atrial exit block in a child with dengue fever. In a study by Leo et al. incidence of different rhythm abnormalities were: sinus bradycardia in 60%, first degree heart block in 11%, and ventricular ectopics in 15% of cases. Low voltage QRS complex and supraventricular tachycardia (SVT) were reported by Sheetal et al but it was not found in our study. This low voltage QRS complex and SVT was ascribed to subacute myocarditis. Chuah et al have described transient ventricular arrhythmias as a cardiac manifestation of dengue fever. We did not observe significant ventricular arrhythmias in our study. On the contrary one patient had developed atrial fibrillation. Obeyesekere et al have described direct cardiac involvement in dengue fever patients as evidenced by positive cardiac biomarkers. Wichmann et al showed that 25% of dengue patients presented with one or more elevated markers of myocardial injury, such as myoglobin, CK-MB, troponin T, NT-proBNP, and/or heart-type fatty acid binding protein levels (h-FABP). In our study quantitative troponin was not elevated in any of our patients. In the study by Gupta et al., systolic dysfunction was absent in all patients and mild diastolic dysfunction was present in 14.28% of cases. However Gupta et al reported that 78.5% of patients with severe dengue in their study had elevated CK-MB level. Diastolic dysfunction was not included in our study but systolic dysfunction was present in four patients (3.3%). Recovery occurred within three months. Transient decrease in ejection fraction, left ventricular wall motion abnormality which improves with time is known to occur in patients with dengue. Similar findings were noted in our study. We could not find any association between severity of dengue fever and cardiac manifestations. Kabra et al. in their study also couldn’t find any correlation between myocardial involvement and severity of dengue fever. There are few reports of acute heart failure during dengue virus infection. In an evaluation of 17 dengue patients with radionuclide ventriculography, Wali et al. showed that 7 patients had an ejection fraction of <40% and 12 had global hypokinesia, and that, after 3 weeks of follow-up, all abnormalities had returned to normal. In our series four patients had left ventricular dysfunction but only two of them presented with heart failure. None of our patients had suffered from cardiogenic shock. Weerakoorn et al. performed autopsies in five patients who died due to dengue complications and showed histopathological evidence of myocarditis. The main histological findings were interstitial edema with inflammatory cell infiltration and necrosis of myocardial fibers and, in one case, evidence of pericarditis.

**Limitations**

It was a single centre study. We did not include different biomarkers like myoglobin, CPK MB, heart fatty acid binding protein. Cardiac MRI is the gold standard for diagnosis of myocarditis which was not included in our study.

**Conclusion**

Cardiac manifestations of Dengue were present in 11.4% of our patients. Incidence vary between 15 to 50% in different series. Bradyarrhythmias were commonest manifestation in our study (6.6%) which resolves spontaneously within seven to fourteen days. Left ventricular systolic dysfunction was present in 3.3% of patients which recovered within three months. Pericardial effusion was less common and it resolved within two weeks. We did not observe significant tachyarrhythmias in our patients except one case of atrial fibrillation.

**References**

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HbA1C in Management of Type II Diabetes Mellitus: A Cross-sectional Survey of Indian Physicians

AK Das¹, G Saxena²*, Swati Naik³

Abstract

Objectives: Hemoglobin A1C (HbA1C) estimation is the standard and commonly used method for diagnosis and monitoring of diabetes therapy. We conducted a questionnaire based survey to understand the Indian physician’s adherence to HbA1C for effectively managing Type 2 diabetes mellitus (T2DM) patients and its influence on the decision making process.

Methods: A validated questionnaire comprising of 10 questions was administered to physicians/endocrinologists at the 44th Annual Conference of RSSDI-2016, Hyderabad. The questions of the survey were designed to understand average cutoff HbA1C level for physicians to start the mono-therapy or combination therapy with or without insulin along with preferred class of Oral anti-diabetic drugs (OAD) in Indian T2DM patients.

Results: 41% physicians selected HbA1C level in between 7.0-7.4% to start mono-therapy while 94.5% chose metformin as the first line OAD. In metformin uncontrolled patients, 56.8% responders chose to start a DPP4 inhibitor. To initiate dual therapy 42.9% responders chose HbA1c level of 8.0-8.4% while for triple therapy 37.1% responders selected HbA1c level of 9.0-9.4%.

Conclusion: This survey shows the management patterns of T2DM patients by Indian physicians are in line with western guidelines especially AACE. Though guidelines do not offer stringent recommendation on first/second add-on class of OADs, DPP4i emerged as preferred choice for mono-therapy in metformin-intolerant patients and as first add-on in patients uncontrolled on metformin alone.

Introduction

Diabetes is one of the leading cause of premature morbidity and mortality globally, mainly due to the increased risk of cardiovascular disease (CVD).1,2 Worldwide more than 415 million adults are suffering from the diabetes which is estimated to reach around 642 million by 2040. Nearly 80% of total adult diabetics are in low or middle income countries.

In India 69 million person are suffering from diabetes. WHO estimates every 26 per 100,000 person die due to diabetes in India.3 Almost every tenth adult (9.3%) in India is estimated to be affected by diabetes. Increasing evidence shows that nearly half of the patients with Type 2 Diabetes mellitus (T2DM) are not aware of their condition. T2DM in India poses a daunting challenge to Indian health care system and its sustainable development. Early diagnosis is crucial as careful diabetes management can reduce long term complications like retinopathy, renal failure, cardiovascular disease and limb amputation.4

Hemoglobin A1C (HbA1C) estimation is the standard and commonly used method for diagnosis and monitoring of diabetes therapy. It relates well to both post prandial blood glucose and fasting Plasma glucose (FPG).5 Guidelines have recommended HbA1c as reference to monitor, intervene or diagnose the disease. The American Association of clinical endocrinologists and American college of Endocrinology (AACE) supports an HbA1C goal of < 6.5% for most patients and a liberal goal of >6.5% if the lower target cannot be achieved without adverse outcomes in T2DM patients.6,7 American diabetes association (ADA) supports HbA1C <7.0% in most patients as glycemic goal but HbA1C < 6.5% in some patients such as young patient with relatively shorter history of the disease, if it can be achieved without adverse outcome.

AACE (American association of clinical endocrinologists) however provides clear HbA1c level to start the mono-therapy and combination therapy. However, ADA (American Diabetes Association) recommends step wise addition of oral anti-hyperglycemic agents if glycemic control is not achieved over the period of time, while not specifying the HbA1c value to start the dual or triple combination.

Though guidelines specify definitive values of HbA1c in T2DM patients for diagnosis, management and monitoring, the extent to which these guidelines that are followed in real life scenario is unknown.

The rationale of this questionnaire based survey is to understand the adherence of HbA1C to effectively manage Indian T2DM patients by Indian physician/ diabetologist/endocrinologist and its influence on the treating physician’s decision making during the management of Indian T2DM patients.

Methodology

This was a questionnaire-based survey of physicians seeing patients of T2DM across different parts of
Delegates attending RSSDI conference were approached, explained the objective of doing the survey and those willing to participate were asked to fill up the questionnaire. The completed questionnaires were collected and analyzed. Number of responses to each question was categorized as percentages for all the responses were calculated. Data were expressed in n (%). Missing data was not considered for calculating percentages.

Results

A total of 337 questionnaires were filled, out of which 310 were included for analysis. 27 questionnaires were not included because of incomplete or illegible responses.

HbA1c value in the newly diagnosed T2DM patients at the time of presentation to the physicians was in the range of 8.5 to 8.9% as opined by 31.3% of surveyed physicians, closely followed by patients presenting with HbA1c value of >9% (Figure 1).

In response to the HbA1c level at which the pharmacotherapy should be started 41% physicians preferred HbA1c level in between 7.0-7.4% to start the mono therapy, followed by HbA1c level of 6.6 to 6.9% (18.4%). Around 17% chose the option to start the dual therapy in all the patients in all patients irrespective of HbA1c value (Figure 2).

Majority of the responders chose metformin as first line Oral hypoglycemic agent (OHA) (94.5%). In metformin intolerant (contraindicated) patients, majority of surveyed physicians preferred to start a DPP4 inhibitor (56.1%) followed by alpha glycosidase inhibitors (5.5%) and thiazolidinedione (5.5%), in patients uncontrolled on metformin (56.8%) responders preferred a DPP4i option, followed by option opted SU with (33.9%) responders choosing SUs as option.

In response to cut off value to initiate dual and triple therapy 42.9% responders chose the HbA1c level of 8.0-8.4% as cut off to initiate dual therapy, followed by HbA1c level of 7.5-7.9% (23.2%) while 37.1% responders selected option of HbA1c level of 9.0-9.4% to initiate the triple therapy and more than 10.0% of HbA1c level to start the basal insulin (37.7%).

More than half (52.6%) responders believed in initiating basal insulin in patients uncontrolled on combination of metformin and a DPP4i. More than a third of responders (37.7%) chose 10.0-10.4% of HbA1c level to initiate the insulin therapy followed by 26.1% responders choosing the HbA1c level of 9.0-9.4% to initiate the insulin therapy.
glycemic control. The amount of HbA1c reflects the glycemic control of a patient during the past 6 – 8 week’s period. The amount of HbA1c correlates well with fasting and postprandial blood glucose levels. At present, HbA1c is the most commonly used surrogate marker for setting goals of treatment.9

Interestingly, in case metformin being intolerable, survey showed that majority of the responders chose to initiate therapy with a DPP4i. Even when tolerability of metformin is not a concern a healthy proportion of respondents (46.8%) chose DPP4i as the second add on to metformin and SU.

Multiple sites of actions and glucose dependent lowering are the hallmarks of incretin based therapy. DPP4is other than being effective in lowering the blood glucose level, have considerably raised the curiosity of the researchers because of their pleotropic effects including potential role in modifying the course of inflammation. DPP4 inhibitors pleotropic effect may result from their action on multiple factors including insulin resistance, oxidative stress, dyslipidemia, adipose tissue dysfunction, dysfunctional immunity, and anti-apoptotic properties of these agents in the heart and vasculature.10

ADA and EASD combined position statement states that if mono-therapy alone does not achieve/maintain an HbA1c target over ~3 months, the next step would be to add a second agent.11,12 It also recommends the addition of one of five anti-hyperglycemic drugs beyond metformin when A1C is above target in a step-wise manner acknowledging their side effects and safety.13

However, DeFrenzo et al14 talks about the pathophysiology approach. It states that in most newly diagnosed diabetic patients, mono-therapy will not reduce HbA1c <6.5–7.0% or, most optimally, <6.0%, and combination therapy will be required.

It further goes on to state that, underlying pathogenic abnormalities if not corrected by anti-diabetic drugs will not achieve long term glycemic control OHA prescribed as combination therapies should have an synergistic effect. Three years into the UKPDS trial (designed as a monotherapy study) it became clear that neither metformin nor SU can prevent the progressive β-cell dysfunction and hence cannot stabilize the HbA1c.15

American association of clinical endocrinologists (AACE) in its glycemic control algorithm extensively uses the presenting HbA1c as a parameter to initiate the pharmacotherapy (mono or in combinations).16 It is recommended by AACE to start mono-therapy when the entry HbA1c is less than 7.5%, dual therapy at the entry HbA1c level of more than 7.5%. This survey has shown that most Indian physicians initiate pharmacotherapy at HbA1c level of 7.0% and above however a significant proportion of physicians (28.1%) preferred the initiation of pharmacotherapy in patients with HbA1c levels between 6.5%-6.9%. Similarly for dual therapy most physicians preferred chose entry level HbA1c of 8.0-8.4% where as a sizeable portion of respondent preferred 7.5%-7.9% entry HbA1c which is more or less in line with AACE recommendations.

If glycemic control is not achieved in 3months with dual therapy AACE recommends further intensification of therapy or addition of insulin. For patients presenting with HbA1c of 9.0% without symptom AACE warrants the triple therapy initiation. In course of this survey for initiating triple therapy most physicians preferred the option of HbA1c entry level of 9.0-9.4%

It shall be noted in context that Indian T2DM patients differs significantly from their global counterparts, in terms of presentation, entry HbA1c level and duration of disease before diagnosis. However, the finding of this survey are more or less in line with AACE glycemic control algorithm as far as the therapy based on entry level HbA1c is concerned.

Though the guidelines do not offer much distinction on the class of OHAs to be preferred especially as first and the second add on. This survey has shown that the preference of Indian physicians in metformin intolerant patients as well as add on to metformin therapy in others is a DPP4 inhibitor.

Being a questionnaire based survey with multiple options to choose against each question this analysis has few limitations including that the actual prescription patterns were not tracked and analyzed based on HbA1c cut-off values. For practical purposes, the survey included direct questions relying on HbA1c level rather than the complete clinical profile and that HbA1c can’t be the only basis for the direction of therapy.

However, whether the approach suggested by majority of responders to start combination therapy based on HbA1c level is beneficial than the stage wise addition of anti-diabetic agents remains to be a subject of debate unless an adequately powered randomized controlled trial (RCT) is carried out to answer this question.

Conclusion

This survey has shown that despite of Indian T2DM patients being significantly different from their western counterparts, the management patterns of Indian T2DM patients by Indian physicians are in line with western guidelines especially AACE and though these guidelines do not offer recommendation on class of OHAs as first and second addition to therapy, DPP4 inhibitors have emerged as preferred choice amongst Indian physicians as combination therapy

![Fig. 4: Preferred alternate OHA options patients intolerant to metformin](image-url)
and as mono-therapy in metformin intolerant patients.

References


14. Pathophysiologic Approach to Therapy in Patients With Newly Diagnosed Type 2 Diabetes Ralph A. DeFronzo, Roy Eldor, Muhammad Abdul-Ghani. Diabetes Care 2013; 36 (Supplement 2) S127-S138; DOI: 10.2337/dc13-201


Prevalence of Metabolic Syndrome in Rheumatoid Arthritis Patients: A Case Control Study from a Tertiary Care Centre in North India

GSRSNK Naidu1, Nilesh Bhilave2, Kusum Sharma3, Indu Verma4, Aman Sharma5

Abstract
Background: Cardiovascular disease (CVD) is the leading cause of mortality in patients with rheumatoid arthritis (RA). Along with traditional cardiovascular risk factors and systemic inflammation, metabolic syndrome (MetS) contributes to CVD and increased mortality in patients with RA. In this study we determine the prevalence of MetS in RA patients presenting to a tertiary care centre in north India.

Methods: This is a case control study involving 114 patients of RA with disease duration of ≥1 year and 114 healthy controls who are age and sex matched. Components of MetS were assessed in all the subjects and disease activity of RA was determined by DAS28-ESR. MetS was defined according to modified ATP-III criteria and consensus definition of metabolic syndrome for adult Asian Indians.

Results: Women constituted 81.6% in RA group and 80.5% in control group. Mean age of subjects was 44.81±12.7 years in RA group and 43.27±12.6 years in control group. According to modified ATP-III criteria, 36 (31.6%) RA subjects and 17 (14.9%) controls had MetS (p=0.03). According to the consensus definition of metabolic syndrome for adult Indian criteria, 40 (35.1%) RA subjects and 18 (15.8%) controls had MetS (P=0.01). There was no significant difference in disease activity between subjects of RA with or without MetS (p=0.276).

Conclusion: The prevalence of MetS was higher in RA subjects compared to controls. There is no association of MetS with disease activity in our cohort. Larger studies are needed to determine the relation between MetS and disease activity.

Introduction
Rheumatoid arthritis (RA) is a chronic, symmetric, inflammatory arthritis of unknown etiology. Extra-articular manifestations are seen in up to 50% of patients with RA.1 Extra-articular manifestations are in the form of rheumatoid nodules, skin ulcers, scleritis, episcleritis, neuropathy, interstitial lung disease, pleural involvement, pericarditis, myocarditis, coronary artery disease (CAD), sicca symptoms, glomerulonephritis, vasculitis and atherosclerotic disease. Cardiovascular disease (CVD) is a major cause of mortality in RA patients and about 50% of mortality in RA could be attributed to cardiovascular disease.2 Apart from the traditional risk factors for CVD, systemic inflammation and metabolic syndrome (MetS) contribute to CVD risk and increased mortality in patients with RA.3

Metabolic syndrome (MetS) describes a constellation of atherosclerotic cardiovascular risk factors such as dyslipidemia, central obesity, insulin resistance, impaired glucose tolerance and hypertension.4 MetS is associated with approximately two fold increased risk for fatal cardiovascular disease (CVD) in men and nonfatal CVD in women in general population.5 Studies from India showed a high prevalence of MetS in general population, varying between 23.9% and 33.5%.6,7 The estimated worldwide prevalence of MetS in RA was 30.65%.8 Two small studies from India, one from northeast India and the other from south India, showed the prevalence of MetS in RA to be 16.7% and 57.4% respectively.9,10

The present study was done to determine the prevalence of MetS in patients with RA from north India and to explore the relationship between MetS and disease activity.

Materials and Methods

Subjects
This is a prospective case control study conducted in a tertiary care centre in north India. The cases included 114 patients diagnosed to have RA (according to 1987 ACR classification criteria for RA) and with a disease duration of more than 1 year.11 The controls group included 114 healthy controls that were matched for sex and age (±5 years). Pregnant females, subjects not consenting to participate in the study were excluded from the study. This study was approved by the institute ethics committee and a written informed consent was obtained from all subjects before enrolling in the study.

Patient assessment
Patient assessment included a structured interview, physical examination, laboratory tests and review of medical records. Details regarding disease duration, extra-articular manifestations, co-morbid conditions (hypertension and diabetes mellitus) and treatment details were noted. Height (cm), weight (kg) and waist circumference (cm) were measured and body mass index was calculated. Blood pressure was determined as the average of two measurements obtained 5 min apart.
after subjects had rested for at least 10 min. Subjects were considered hypertensive if they were taking antihypertensive agents or if they had a systolic blood pressure of more than 130mmHg or a diastolic pressure of more than 85mmHg. In patients, disease activity was measured using the Disease Activity Score-28 ESR (DAS28-ESR). DAS28-ESR of less than 2.6 was considered remission, score between 2.6 and 3.2 was considered low activity, score more than of 3.2 and less than 5.1 was considered moderate activity and score more than 5.1 was considered high disease activity.

**Laboratory tests**

Blood was collected after an overnight fast (8-12 hours) for the measurement of a complete blood count, urea, creatinine, liver enzymes, serum bilirubin, serum total proteins, serum albumin, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides and low-density lipoprotein (LDL) cholesterol. In patients with RA, CRP and ESR (by Westergren’s method) were measured. Serum fasting glucose and lipid profile (cholesterol, triglycerides and low-density lipoprotein) were measured after an overnight fast (8-12 hours) for the diagnosis of MetS.

**Table 1: Definitions of metabolic syndrome used in the study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NCEP ATP-III definition modified for asians</th>
<th>Consensus definition of MetS for adult asian Indians</th>
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<tr>
<td>Waist circumference</td>
<td>≥90 cm for men ≥80 cm for women</td>
<td>≥90 cm for men ≥80 cm for women</td>
</tr>
<tr>
<td>Serum Triglycerides</td>
<td>≥150 mg/dl</td>
<td>≥150 mg/dl</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&lt;40 mg/dl for men &lt;50 mg/dl for women</td>
<td>&lt;40 mg/dl for men &lt;50 mg/dl for women</td>
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<tr>
<td>Fasting glucose</td>
<td>≥110 mg/dl</td>
<td>≥100 mg/dl</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130 mmHg systolic pressure ≥285 mmHg diastolic pressure</td>
<td>≥130 mmHg systolic pressure ≥285 mmHg diastolic pressure</td>
</tr>
</tbody>
</table>

HDL: High Density Lipoproteins; MetS: Metabolic Syndrome; NCEP ATP-III: National Cholesterol Education Program, Adult Treatment Panel III

**Table 2: Baseline characteristics of RA patients and controls**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cases (n=114)</th>
<th>Controls (n=114)</th>
<th>P value</th>
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<tr>
<td>Age (mean±SD) years</td>
<td>44.8±12.7</td>
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<tr>
<td>Female: Male</td>
<td>93±21</td>
<td>92±22</td>
<td>0.866</td>
</tr>
<tr>
<td>Deformities</td>
<td>32.5% (n=37)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
<td>6.1% (n=7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Skin rash</td>
<td>2.6% (n=3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sicea symptoms</td>
<td>5.3% (n=6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>RF positivity</td>
<td>78.1% (n=89)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>High CRP</td>
<td>86% (n=96)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.9±23.3</td>
<td>156.8±28.7</td>
<td>0.895</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>60.8±12.2</td>
<td>59.1±9.9</td>
<td>0.244</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>25.5±5.2</td>
<td>24.2±3.0</td>
<td>0.005</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>92.1±20.1</td>
<td>81.2±9.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

FBG (mg/dl) 95.3±26.7 97.8±21.6 0.079
S. triglycerides (mg/dl) 152.2±67.2 135±50 0.039
Cholesterol LDL (mg/dl) 98.7±29.7 100.9±27.7 0.320
HDL (mg/dl) 47.4±11 41±12.6 <0.001
Total cholesterol (mg/dl) 168.2±39.2 164.8±39.2 0.526
SBI (mmHg) 124.9±16.7 119.4±10.7 0.018
DBP (mmHg) 80.5±9.9 75.3±7.4 <0.001
BMI: Body Mass Index; CRP: C-Reactive Protein; HDL: High Density Lipoproteins; LDL: Low Density Lipoproteins; RF: Rheumatoid Factor

**Results**

**Demographic characteristics**

Out of 114 patients with rheumatoid arthritis, 93 (81.6%) were women and 21 (18.4%) were men, with a mean (±SD) age of 44.8±12.7 years. Among the controls, 92 (80.7%) were women and 22 (19.3%) were men, with a mean (±SD) age of 43.2±12.6 years. Age (p=0.36) and sex (p=0.866) were matched in both the groups. Rheumatoid factor was positive in 89 (78.1%) patients while CRP was elevated in 96 (86%) patients.

Deformities were noted in 37 (32.5%) patients with RA while rheumatoid nodules were seen in only 7 (6.1%) patients with RA.

Compared to controls, patients with RA had significantly more BMI (25.5±5.2 kg/m² vs 24.2±3.5 kg/m², p=0.005) and waist circumference (92.1±20.1 cm vs 81.2±9.9 cm, p=0.001). The mean fasting blood glucose was 95.3±26.7 mg/dl in RA patients and 97.8±21.6 mg/dl in controls (p=0.079). In RA patients, mean serum triglycerides (152.2±67.2 mg/dl vs 135±50 mg/dl, p=0.039) and HDL cholesterol (47.4±11 mg/dl vs 41±12.6 mg/dl, p<0.001) were significantly more than the controls. Both the mean systolic blood pressure (124.9±16.7 vs 119.4±10.7 mmHg, p=0.018) and mean diastolic blood pressure (80.5±9.9 vs 75.3±7.4 mmHg, p<0.001) were significantly more in RA patients compared to controls. Baseline characteristics of RA patients and controls are shown in Table 2.

**Prevalence of metabolic syndrome**

According to modified ATP-III criteria, 36 (31.6%) RA subjects and 17 (14.9%) controls had MetS. The prevalence of MetS between the two groups was statistically significant (p=0.03). According to the consensus definition of metabolic syndrome for adult Indian criteria, 40 (35.1%) patients with RA and 18 (15.8%) controls had MetS and the difference was statistically significant (p=0.01). The details of criteria fulfilled by patients of MetS are shown in Table 3.

**Correlation of disease activity and metabolic syndrome**

Among the 36 RA patients with MetS according to modified ATP-III criteria, 25 patients had very high disease activity (DAS28-ESR>5.1), 6 patients had moderate activity (DAS28-ESR 3.2-5.1) and 5 patients had low disease activity (DAS28-ESR 2.6-3.2). There was no significant difference in disease activity between patients of RA with or without MetS (p=0.276). Out of 40 patients with RA and MetS according to consensus definition of metabolic syndrome for adult Asian criteria, 29 patients had very high disease activity, 6 patients had moderate activity and 5 patients had low disease activity. None of the patients with MetS were in remission (DAS28-ESR<2.6) at the time of assessment. There was no significant difference in disease activity...
Cardiovascular disease is a major cause of mortality in patients with RA. Apart from the presence of traditional risk factors for CVD, presence of systemic inflammation and MetS in patients with RA contributes to increased CVD incidence and mortality in these patients. We included 114 patients of RA with disease duration of more than one year and determined the prevalence of MetS syndrome in them and compared with the prevalence of MetS in age and sex matched healthy controls.

In our cohort, the prevalence of MetS was 31.6% in RA patients according to modified ATP-III criteria and the prevalence was slightly more (35.1%) when consensus definition of metabolic syndrome for adult Asian Indians was used. The prevalence of MetS in controls was 14.9%, which was significantly lower compared to RA patients. In a study among northeast India, Dihingia et al. have noted that the prevalence of MetS among RA patients was 16.7% according to ATP-III criteria, which was much lower than that seen among our patients. Among the south Indian patients with RA, the prevalence of MetS, according to ATP-III criteria, was 57.4%, much higher than that noted in our patients. These differences in the prevalence of MetS could be due to geographical and racial variations in the prevalence of the components of MetS. Both these studies from India did not consider the consensus definition of metabolic syndrome for adult Asian Indian criteria for MetS, which takes fasting blood glucose of >100mg/dl as the cutoff instead of >110mg/dl in the modified ATP-III criteria. In a meta-analysis by Hallajzadeh et al., the worldwide pooled prevalence of MetS in RA was 31.55% according to the NCEP ATP-III criteria, which is similar to that seen in our cohort of patients.

MacMohan et al. have shown previously that patients of RA had higher levels of pro-inflammatory LDL levels compared to the controls. Similar results were also noted in the Indian patients of RA by Dihingia et al. Even though we have not measured pro-inflammatory HDL levels in our cohort, the mean total HDL cholesterol levels were higher in RA patients compared to controls (47.4±11mg/dl vs 41±12.6mg/dl, p=0.001). Pro-inflammatory HDLs enhance the inflammatory responses by their inability to prevent oxidation of LDL in vessel wall which leads to recruitment of monocytes in to the vessel wall subendothelial space.

We did not find any significant difference in the disease activity, as measured by DAS28-ESR, among RA patients with or without MetS. Even, Dihingia et al. from India and Rostom et al. from Morocco have shown no association between presence of MetS and disease activity in RA patients. However, Tantayakom et al. from Thailand have shown that low cumulative disease activity significantly reduced the risk of having MetS. Karvounaris et al. from Greece also showed that prevalence of MetS was higher in patients with high disease activity.

The major limitation of our study is that it is a case control study involving a less number of patients and controls. A larger cohort of RA patients needs to be prospectively followed up to determine the incidence and the cumulative prevalence of MetS in RA patients and to know their long term cardiovascular outcomes.

In conclusion, prevalence of MetS among RA patients from north India is higher than that seen in controls. However, there is no association of MetS with disease activity in our cohort. More studies with large number of patients of RA needs to be conducted to determine the association between MetS and disease activity scores.

### References


### Table 3: Metabolic syndrome criteria fulfilled by RA patients and controls

<table>
<thead>
<tr>
<th>Number of criteria fulfilled</th>
<th>Modified ATP-III</th>
<th>Consensus definition of MetS in adult Asian Indians</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 RA</td>
<td>16 (14%)</td>
<td>15 (13.2%)</td>
</tr>
<tr>
<td>Controls</td>
<td>21 (18.4%)</td>
<td>21 (18.4%)</td>
</tr>
<tr>
<td>1 RA</td>
<td>45 (39.5%)</td>
<td>45 (39.5%)</td>
</tr>
<tr>
<td>Controls</td>
<td>45 (39.5%)</td>
<td>40 (35.1%)</td>
</tr>
<tr>
<td>2 RA</td>
<td>17 (14.9%)</td>
<td>14 (12.3%)</td>
</tr>
<tr>
<td>Controls</td>
<td>31 (27.2%)</td>
<td>35 (30.7%)</td>
</tr>
<tr>
<td>3 RA</td>
<td>24 (21.1%)</td>
<td>24 (21.1%)</td>
</tr>
<tr>
<td>Controls</td>
<td>12 (10.5%)</td>
<td>11 (9.6%)</td>
</tr>
<tr>
<td>4 RA</td>
<td>11 (9.6%)</td>
<td>14 (12.3%)</td>
</tr>
<tr>
<td>Controls</td>
<td>5 (4.4%)</td>
<td>7 (6.1%)</td>
</tr>
<tr>
<td>5 RA</td>
<td>1 (0.9%)</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Controls</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

ATP-III: Adult Treatment Panel III; MetS: Metabolic syndrome; RA: Rheumatoid Arthritis; between patients of RA with or without MetS (p=0.107).
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Dyslipidemia and Fat Distribution in Normal Weight Insulin Resistant Men

Vivek Patwardhan¹, Anuradha Khadilkar²*, Shashi Chiplonkar¹, Vaman Khadilkar¹

Abstract
Background: Although less common, insulin resistance and deranged lipids are also observed in normal weight individuals. Few studies have assessed body composition and lipid profiles in normal weight insulin resistant individuals.

Objective: To assess differences in body composition and lipid profile in normal weight and overweight 40-60 years apparently healthy men with special reference to insulin resistance.

Design: Cross-sectional observational study in apparently healthy men (40-60 yrs) was performed. Anthropometry, body composition (Dual Energy X-ray Absorptiometry scan), biochemical parameters (lipids, sugar and Insulin) were assessed. HOMA_IR was calculated. Subjects were grouped based on BMI and HOMA-IR for comparison.

Results: Of the 286 subjects 152 (53%) had BMI < 25 (group A) and 134 (47%) had BMI > 25 (group B). Homa-IR was more than 3 in 18% in and in 36% in B. Group B had significantly higher fat, waist circumference, systolic blood pressure, insulin and HOMA-IR. In subgroup analysis in group A, subjects with HOMA IR>3 (group A2) had significantly higher BMI, waist, TG, TG: HDL ratio, android and total fat and lower HDL as compared sub-group A1(HOMA IR<3) (p< 0.05). Mean BMI, waist circumference and systolic blood pressure were significantly higher in B2 than A2 group (p< 0.05). Although total, android and gynoid fat percentage were significantly higher in group B2, android to gynoid ratio was significantly higher in A2 (p< 0.05).

Conclusions: No significant difference in lipids and fat distribution between insulin resistant and non-resistant subjects in overweight groups suggests that insulin resistance in overweight may be an extension of the pathological state related to obesity. In contrast, significant differences in lipid and fat distribution in normal weight insulin resistant individuals may likely be due to a different mechanism.

Introduction

Obesity has been traditionally known as a risk factor for the development of insulin resistance and type II Diabetes Mellitus. Important mechanisms explaining pathogenesis of obesity related insulin resistance are either related to altered adipokines (hormones secreted by adipose tissue) secretion or to inflammatory substances released from adipose tissue macrophages.¹ Increased adipose mass in obesity could lead to pathological changes in adipocyte hormone (adipokines) secretion which regulates insulin sensitivity.

Deficiency of leptin, adiponectin and excess of resistin are associated with increased insulin resistance. Increased adipose tissue macrophages in obesity produce tissue necrotic factor-α (TNF-α), plasminogen activator inhibitor-1 (PAI-1), interleukin-6 (IL-6) and suppressor of cytokine signalling (SOCS) proteins which have ability to induce systemic inflammation. Systemic chronic inflammation has been proposed to have an important role in the pathogenesis of obesity related insulin resistance.¹

Although less common, insulin resistance and diabetes are also observed in normal weight individuals. Normal weight diabetics have been reported to have male preponderance, higher prevalence of microvascular complications, higher prevalence in Asians and have a higher prevalence of insulin use.² Four Studies have shown that adults who have normal weight at the time of diabetes detection experienced higher mortality than overweight adults or overweight adults with diabetes.³ In the absence of obesity, mechanisms contributing to impaired insulin signalling are much less well characterized. The inflammatory responses which are seen in overweight due to fat accumulation are less likely to be applicable in normal weight individuals.

In overweight individuals, regional distribution of body fat is reported to be more important than excessive adiposity in driving the CVD risk.⁴ Thus, apart from anthropometric parameters like BMI and waist circumference it is important to understand distribution of fat by using imaging techniques such as Dual Energy X-ray Absorptiometry (DEXA scan) or Magnetic Resonance Imaging. However, little is known about the body composition of normal weight individuals with insulin resistance.

Insulin-resistance is known to induce characteristic alterations in lipid profile which includes elevation of triglycerides (TG), reduction of HDL-cholesterol (HDL-C) and normal or slightly elevated LDL-cholesterol (LDL-C).⁵ Fasting hypertriglyceridemia occurs because of either increased production of very low-density lipoproteins (VLDL) in fasting state.
by liver or its reduced catabolism. Increase in VLDL production occurs in state of insulin resistance as synthesis of glycogen and glucose utilisation by skeletal muscles is reduced. Hydrolysis of TG from VLDL into glycerol and fatty acids occurs primarily in adipose tissue and muscle where fatty acids are utilized for storage and for energy generation respectively. Although the effect of insulin resistance in overweight individuals has been extensively studied, reports on the effect of insulin resistance on lipid profile in normal weight individuals and comparison between overweight and normal weight individuals are scarce. As lipid profiles in peri-menopausal females would likely be affected by changes in hormonal concentrations, this study was planned in men.

Thus, considering the above together, it is important to study normal weight and overweight individuals with reference to insulin resistance, body composition and their lipid profile. Hence, the objective of our study was to assess differences in body composition and lipid profile in normal weight and overweight 40-60 years apparently healthy men with special reference to insulin resistance.

Materials and Methods

In a cross-sectional observational study, apparently healthy men (40-60 yrs) from routine health checks at hospitals, social groups and private establishments in Pune were invited to voluntarily participate in the study from May 2013 to June 2014. Inclusion criteria were apparently healthy men between 40-60 years who were willing to participate in the study. Subjects with known diabetes, liver, renal, thyroid or cardiac disorders were excluded from the study. Specific exclusion criteria were i) fasting blood sugar level (FBSL) >125 mg/dl, ii) abnormal glutamic pyruvic transaminase (SGPT >65 IU/L), iii) abnormal creatinine (>1.2 mg/dl). Eligible 286 subjects (mean age 49.3±6.4 yrs) out of screened 300 subjects were included in the study with a written informed consent. An ethical approval for the study was obtained from the institutional Ethics Committee. Clinical examination of all study subjects was performed by a physician to assess their health status. Detailed past and present medical histories were recorded.

Anthropometric measurements

Height was measured to the nearest 0.1 cm using Leicester height meter, Child growth foundation, UK, (range 60-207 cm), Weight was measured on an electronic digital scale to the nearest 0.1 kg. Body mass index was computed as weight in kg / height in meter square.

DXA scan

Body composition was measured using Lunar DPX-PRO total body pencial beam Densitometer (GE Healthcare, WI) using a medium mode scan (software encore 2005 version 9.30.044). The precision of the DPX-PRO for repeat measurements in adults is 1.89% for total fat percentage. Region definition for android fat was from the top of ilium superiorly 20% of distance from the ilium to body of mandible and gynoid fat was from top of ilium inferiorly 1.5 times height of android region.

Biochemical Estimations

A venous blood sample (8 ml) was collected between 7 to 9:00 am from each subject after an overnight fast for more than 12 hours using vacutainers (BD Franklin lakes NJ USA). Serum was separated after centrifugation at 2500 rpm for 15 minutes at room temperature within two hours of collection. Fasting blood sugar (FBS), serum creatinine (CR) and SGPT (alanine aminotransferase, ALT) were measured (Glucose was performed by hexokinase method, creatinine by Jaffe method without deproteinization and SGPT by an enzymatic method).

High density lipoprotein cholesterol (HDLC) total cholesterol (TC) and triglycerides (TG) were measured (enzymatic method). Low density lipoprotein cholesterol (LDLC), very low-density lipoprotein cholesterol (VLDL) concentrations were calculated using Friedewald equation.

Insulin was estimated using DRG diagnostics, Germany, ELISA kit.

HOMA-IR was calculated using formula:

\[
\text{HOMA-IR} = \frac{\text{Fasting insulin (µIU/ml)} \times \text{Fasting glucose (mg/dl)}}{405}
\]

Study subjects were divided primarily into two groups based on their BMI as normal weight (Group A, BMI <25) and overweight (group B, BMI >25). Based on HOMA IR, Groups A and B were further sub grouped into A1 (HOMA-IR <3), A2 (HOMA-IR > 3) and B1 (HOMA-IR <3), B2 (HOMA-IR > 3) respectively. WHO criteria were used for BMI grouping. In the absence of a national consensus on the normal cut off values for HOMA-IR, 75th percentile of HOMA-IR (HOMA-IR 3) was considered as the cut off.

Statistical Methods

Data were analyzed using the SPSS software for Windows (version 16.0, 2001, SPSS Inc., Chicago, IL). Normality of the variables was tested using one sample Kolmogorov-Smirnov test before performing statistical analysis. Continuous variables were presented as mean with standard deviation for normally distributed variables. One-way ANOVA was used to examine differences in means between groups.

Results

Of the 286 eligible participants, 152 (53%) had BMI < 25 and 134 (47%) had BMI > 25. Homa-IR was more than 3 in 18% of lower BMI category subjects and in 36% of higher BMI subjects.

In groups based on BMI (A (BMI <25) vs B (BMI >25)), group B had significantly higher fat, waist circumference, systolic blood pressure, insulin and HOMA-IR. There was no significant difference in TC, TG and LDL-C, however, the HDL-C was significantly lower in group B (p< 0.05) (Table 1).

In subgroup analysis, subjects in subgroup A2 had significantly higher BMI, waist, TG, TC: HDL ratio, android and total fat and lower HDL as compared sub-group A1 (p< 0.05). While significant difference was observed only in SBP between sub-group B1 and B2 (p<0.05) (Table 2).

When subjects in sub-group A2 and B2 were compared, the mean BMI, waist circumference and systolic blood pressure were significant higher in sub-group B2 than the sub-group A2 (p< 0.05). Although total, android and gynoid fat percentage were significantly higher in sub-group B2, android to gynoid ratio was significantly higher in subgroup A2 (p< 0.05). Both these groups had comparable lipid parameters (Table 2).
**Discussion**

Our results indicate that overweight subjects (Group B) had significantly higher body fat percent, waist circumference and systolic blood pressure, serum insulin, HOMA-IR and significantly lower HDL-C as compared to normal weight subjects (Group A), but there were no significant differences in TC, TG and LDL-C between these groups (A vs B) indicating insignificant influence of body weight on lipid parameters except HDL-C. Significant differences were observed in TG, HDL, TG: HDL ratio, TG: LDL ratio, LDL: HDL ratio and android fat between insulin sensitive and insulin resistant normal weight subjects (A1 Vs A2), but not in overweight subjects (B1 vs B2). Further, higher percentage of A2 had abnormal lipid profile than of A1. However, no such difference in lipid levels was observed between overweight subjects with (B2) or without (B1) insulin resistance.

Fasting hypertriglyceridemia occurs because of either increased production of VLDL in fasting state by liver in presence of insulin resistance with suboptimal glucose uptake by cells. This is the possible reason for higher TG levels in both insulin resistant groups (A2 and B2). Hydrolysis of TG from VLDL into glycerol and fatty acids occurs primarily in adipose tissue and muscle where fatty acids are utilized for storage and for energy generation respectively. Additionally, in A2 group, as there is possibly less adipogenesis and thus less utilization of VLDL, they possibly had the highest levels of TG and TG: HDL ratio.

Highest android to gynoid fat ratio was seen in A2 as compared to the other groups (A1, B1, B2). This may primarily be due to reduced gynoid fat percentage in A2 rather than an increase in android fat, which was significantly higher in B1 and B2 as compared to A2.

At cellular level, activation of c-Jun N-terminal kinase (JNK) pathway leading to increase in IRS-1 serine phosphorylation and subsequent inhibition of insulin receptor-insulin receptor substrate-1 phosphatidylinositol 3-Kinase- protein kinase B-glucose transporter4 (IR-IRS-1-PKB-GLUT4) pathway is a suggested mechanism of insulin resistance. In overweight individuals, inflammatory mediators like TNF-alpha and Interlukin-6 (from expanding...
adipose tissue, reduced leptin), adiponectin and increased resistin induce activation of JNK pathway. Obesity related inflammatory factors and adipokines are less likely to be responsible for insulin resistance in normal weight subjects.

Among other important inducers of JNK pathway, di-acyl-glycerol (DAG) may be a possible mechanism for insulin resistance in normal weight individuals. Increased intramyocellular lipid (IMCL) levels have been reported in insulin resistant normal weight populations. Factors responsible for utilization of lipids in muscles include lipolytic enzymes Adipose Triglyceride Lipase (ATGL), Hormone-Sensitive Lipase (HSL), membrane proteins like perilipin and mitochondria. ATGL specifically performs the hydrolysis of tri-acyl-glycerol (TAG) into di-acyl-glycerol (DAG). Hormone-sensitive lipase is responsible for DAG hydrolysis. HSL deficiency is shown to accumulate DAG (which is an inducer of JNK pathway) and is also known to reduce adipogenesis (Figure 3). In our study, considering that the A2 group (BMI<25, IR>3) had a lesser fat mass than B2 (BMI>25, IR>3), mechanism related to lipid overload by higher supply of fatty acids (FA) or adipokines and adipose tissue inflammatory mediators are less likely to have a role in developing insulin resistance. So, the possible reason for insulin resistance in A2 groups could be inefficient intramyocellular lipolysis and collection of DAG.

A study in Old Order Amish participants with mutation in LIPE gene, which encodes hormone-sensitive lipase (HSL), has shown that carriers of the mutation had dyslipidemia, hepatic steatosis, systemic insulin resistance, and diabetes. In adipose tissue, this absence of HSL protein resulted in small adipocytes, impaired lipolysis and insulin resistance, altering the regulation of pathways influencing adipogenesis, insulin sensitivity, and lipid metabolism. (Jessica S. Albert, 2009) encoding hormone-sensitive lipase (HSL). The impairment of adipogenesis in humans with the HSL mutation exhibits site specificity; certain fat depots are affected (e.g., subcutaneous fat in different locations), while others are not (e.g., visceral fat).

Thus, in normal weight insulin resistant individuals, possibly the deficiency of HSL leading to inability to accumulate non- android fat may have resulted in high TG and high TG: HDL ratio. Similarly, HSL deficiency may lead to intramyocellular DAG accumulation and maybe be responsible for insulin resistance.

Study limitations include that we have not been able to estimate the enzyme/ gene for HSL. Further, markers of inflammation such as TNF-alpha and Interleukin-6 were not assessed. Nevertheless, our study suggests that normal weight insulin resistant individuals have significant lipid and fat distribution abnormalities. Further studies are required to explore alternate mechanisms of insulin resistance including HSL deficiency in this group.

**Conclusion**

No significant difference in lipids and fat distribution between insulin resistant and non-resistant subjects in overweight groups suggests that insulin resistance in overweight may be an extension of the pathological state related to obesity. In contrast, significant differences in lipid and fat distribution in normal weight insulin resistant individuals may likely be due to a different mechanism. Insulin resistance and a deranged lipid profile in normal weight individuals warrants urgent attention.

**References**

A Study of Correlation between Apolipoprotein B and Dyslipidemia in Type 2 Diabetes Patients and its Relation with Proteinuria- A Tertiary Care Hospital Based Study

Surendra Kumar¹, Rajesh R², Nitin Sharma³, Chandrashekhar Bhandiwad³, Chandreshwar Pratap Singh³, Vipin Singhal⁴, Ashish Chakranarayan⁴, Narendra Kumar Dara⁵

Abstract

Objectives: Individual with diabetes may have several from of Dyslipidemia. Dyslipidemia has been considered to be factor that plays a risk in progression of micro vascular disease, especially in diabetes.¹ The present study is intended to Study of correlation between Apolipoprotein B and Dyslipidemia in type 2 diabetes patients and prevalence of dyslipidemia in type 2 diabetic patients.

Material and Methods: Prospective cross- sectional study conducted on 100 cases of type 2 diabetes mellitus. Groups are divided according to A/C ratio and association of dyslipidemia was seen. Serum Apolipoprotein B was measured using immunoturbidimetric method.

Results: Pearson’s correlation analysis of Apo B with lipid parameters in diabetic patients showed that, LDL, TC and Tg were positively correlated with Apo- B. There was a positive and linear correlation between LDL and Tg. Apo- B was negatively correlated with HDL-C.

Conclusion: The majority of patients studied had low HDL-C, elevated non HDL- C, elevated total cholesterol, elevated triglycerides, elevated LDL -C and elevated apo B. Apolipoprotein B had a positive linear correlation with total cholesterol, triglycerides, LDL-C, non-HDL-C. The strongest positive correlation was with non-HDL-C. Patients with low HDL-C had high apo B levels.

Inclusion Criteria

• Age of patient < 70 year
• All patients of diabetes diagnosed fasting glucose of >126 mg/dL, 2 hr glucose load >200 mg/dL with symptoms and HbA1c >6.5 (ADA2017).
• Type 2 diabetes after 5 yrs of diagnosis. HbA1c 6-7.5 gm%.

Exclusion Criteria

• Patients take lipid lowering drugs within 6 weeks and weight reducing diet.
• Patients with hypothyroidism, familial dyslipidemia, familial hypercholesterolemia, alcoholics to avoid false increase in apolipoproteins.
• Patients with fever, UTI, CHF (false albuminuria).
• Type 2 DM <5 yrs of diagnosis.
• Age > 70 yr.
• Patients on dialysis.
• Smokers.
• Inherited renal disease and connective tissue disorder.
• Poorly controlled hypertension.

All the patients were asked to come in diabetic care and research center, PBM hospital Bikaner after an overnight fasting (≥8 hours). Blood collection was done clean venepuncture of a large antecubital vein using a 19 gauge needle after taking all aseptic precautions. Sample collection tubes containing direct thrombin inhibitor was used. Groups are divided according to A/C ratio as follows- no proteinuria <30mg/dl, incipient proteinuria (30-300mg/dl) and overt proteinuria (>300mg/dl) and association of dyslipidemia was seen.

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defect in insulin secretion, insulin action, or both. Type 2 diabetes the most prevalent form of the disease, is often asymptomatic in its early stages and can remain undiagnosed for many years.² The diagnosis of T2DM as currently outlined by the American Diabetes Association (ADA), is based on an HbA1c ≥ 6.5%, or fasting plasma glucose level ≥ 126 mg/dL during an oral glucose tolerance test, or the presence of classical symptoms of hyperglycemia (polyuria, nocturia, polydipsia,etc.) and a random plasma glucose ≥ 200 mg/dL. ApoB is the structure protein of all proatherogenic lipoproteins. ApoB100 is the only lipoprotein that does not transfer among lipid particles and is the only lipoprotein that could be elevated even in diabetic normolipidemic patients.⁴ Thus it provides the best estimate of the total number of atherogenic particulars even in the absence of hyperlipidemia. Therefore a well organised systemic approach, carried out to find any correlation between Apolipoprotein B and dyslipidemia in type 2 Diabetes patients.

Material and Methods

Prospective study was conducted in department of Medicine and PBM hospital Bikaner. Total 100 cases of type 2 diabetes mellitus having age between 20 yrs to70 yrs were selected for the study.
The cross-sectional study was conducted on 100 patients of type 2.18%, 4%, 62% and 63% patients had abnormal total cholesterol, triglyceride, HDL, LDL respectively. Total 77 patients were found having Hba1c <7.0% and out of them 51.9%, 12.9%, 12.1%, 12.9% and 3.8% had normal albuminuria, micro-Low-albuminuria, micro-high-albuminuria, overt-low-albuminuria and overt-high-albuminuria respectively while only 3 patients were found having low density lipoprotein level ranges between 146-175 mg/dl and out of them 6.6%, 46.6%, 20% and 26% had micro-Low-albuminuria, micro-high-albuminuria, overt-low-albuminuria and overt-high-albuminuria respectively. The difference was statistically significant (p value-0.0001) (Table 4).

Total 63 patients were found having high density lipoprotein level <40 mg/dl and out of them 33%, 17.4%, 28.5%, 9.5% and 11.1% had normal albuminuria, micro-Low-albuminuria, micro-high-albuminuria, overt-low-albuminuria and overt-high-albuminuria respectively while 36 patients were found having high density lipoprotein level ranges between 40-50 mg/dl and out of them 72.2%, 5.5%, 19.4% and 2.7% had normal albuminuria, micro-Low-albuminuria, micro-high-albuminuria and overt-low-albuminuria respectively. Only 1 patient was found having high density lipoprotein >50 mg/dl and that belong to overt-high-albuminuria The difference was statistically significant (p value-0.0001) (Table 5).

Total 31 patients were found having Apo-B level ranges between 90-99 and out of them 96.7% and 3.2% had normal albuminuria, micro-high-albuminuria respectively while 11 patients were found having Apo-B level ranges between 100-119 and out of them 90.9% and 9% had normal albuminuria and micro-Low-albuminuria respectively.

11 patients were found having Apo-B level ranges between 120-139 out of them 63.6%, 18.1% and 18.1% had normal albuminuria, micro-low-albuminuria, micro-high-albuminuria respectively while 31 patients were found having Apo-B level ranges between 140-159 and out of them 29%, 64.5% and 6.4% had micro-Low-albuminuria, macro-low-albuminuria and overt-low-albuminuria respectively. 11 patient had Apo-B level ranges between 160-179 and out of them 9%, 45.4% and 36.3% had micro-low-albuminuria, macro-high-albuminuria,
microalbuminuria in patients. 12-14 a predictor of rapid progression of and low HDL cholesterol levels) is consistent with this earlier study also increasing severity of proteinuria. In mean high density lipoprotein with low density lipoprotein and decreasing trend of total cholesterol, triglycerides, albuminuria. 7

male dominance in the prevalence of diabetes mellitus and were under treatment. diagnosed as having type 2 diabetes is important for patients at risk detection and correction of anaemia in patients with a normal ACR to 29% of proteinuria increasing degree of anaemia increases it is evident from study conducted by Adetunji et al, who reported that There was a rise in the prevalence of anaemia from 19% in patients with a normal ACR to 29% in those with microalbuminuria and to 41% in macroalbuminuria. This increase in the prevalence of anaemia in microalbuminuria compared to normoalbuminuria was not explained by declining renal function as there was no significant difference in eGFR between the two groups. Anaemia was common in the study population. Early detection and correction of anaemia in diabetes is important for patients at risk of impaired quality of life and increased cardiovascular risk. 19

Here, cases were divided according to creatinine level in relation to severity of proteinuria. Buch et al studied kidney function parameters like serum creatinine and blood urea. Both serum creatinine and blood urea were higher in males and in patients with positive microalbuminuria. This can be explained and co related with poor glycemic control in both these groups. In their study group few patients with diabetic nephropathy and few who were on dialysis had very high values of serum creatinine and blood urea and this was the reason behind significantly high standard deviation of the values of blood urea and serum creatinine. Over time, high blood sugar levels damage millions of nephrons - tiny filtering units within each kidney. As a result, kidneys are unable to maintain the fluid and electrolyte homeostasis. Creatinine is filtered by the Glomerulus; therefore, serum creatinine level is used as an indirect measure of glomerular filtration

As glomerular filtration rate (GFR) diminishes, there is a rise in plasma concentrations of serum creatinine and urea.

Furthermore, this rise indicates progression of diabetic nephropathy and estimation of serum creatinine has
greater prognostic ability compared with urea for predicting the adverse outcomes.16 Therefore, raised serum urea and creatinine levels in diabetics clearly indicate that prolonged hyperglycaemia causes irreversible damage to nephrons of kidney. Raised serum creatinine and reduced GFR has become firmly entrenched as fairly reliable indicators of kidney dysfunction. The overall prevalence of hyperglycaemic control, blood urea and serum creatinine are important risk factors for the development of microalbuminuria.17 In our study Apo- B level increases with severity of proteinuria. In line with this Chan et al also found increasing trend in Apo-B level with increases in severity of proteinuria. They found that patients with abnormal albuminuria had higher mean serum apo B concentrations than normalalbuminuric patients. Albuminuria correlated with apolipoprotein B (apo B) (r = 0.25, p = 0.003). These close associations may contribute to the increased cardiovascular risk in Chinese NIDDM patients with abnormal albuminuria.18

Watts et al also found that diabetic patients with persistent microalbuminuria had significantly higher concentrations of apo B (p < 0.01), but a lower concentration of HDL cholesterol (p < 0.05). No significant differences were found in serum lipids and lipoproteins between diabetic patients with normal albumin excretion and non-diabetic subjects.19

There was a robust correlation between Apo-B and lipid parameters in diabetic patients. There was a positive and linear correlation between LDL and Tg. Apo-B was negatively correlated with HDL-c.

A study by Wambugu also found same type of trend between Apo-B and lipid profile in type 2 diabetes. He found positive correlation between Apo B and total cholesterol (P-value of <0.01). Most of the patients with high total cholesterol were also likely to have high apo B levels.

There is a good correlation between Apo B and LDL-C with a P value of <0.01. Patients with high Apo B levels were also likely to have high LDL-C levels. There is good correlation between Apo B and triglycerides (P value <0.01). Most of the patients with high triglycerides were also likely to have high Apo B levels. He also reported that there is no correlation between Apo B and HDL-C (P value 0.114). This is because most of the patients with high Apo B have low HDL-C levels.20

**Summary**

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Type 2 diabetes, the most prevalent form of the disease, is often asymptomatic in its early stages and can remain undiagnosed for many years.21 Diabetic patients have a greater likelihood of having dyslipidemia, hypertension and obesity. Individuals with DM have an increased risk of progressing to renal disease.

The majority of patients studied had low HDL-C, elevated non-HDL-C, elevated total cholesterol, elevated triglycerides, elevated LDL-C and elevated apo B. Apolipoprotein B had a positive linear correlation with total cholesterol, triglycerides, LDL-C, non-HDL-C. The strongest positive correlation was with non-HDL-C.

Patients with low HDL-C had high apo B levels. Apo B can help identify additional dyslipidaemic phenotypes in patients with normal cholesterol and normal LDL-C. Apo B levels correlated positively to the degree of nephropathy.

**References**

Four-year Incident Neuropathy and its Risk Factors in Subjects with Type 2 Diabetes

Sangeetha Srinivasan¹, Rajiv Raman²*, Vaitheeswaran Kulothungan³, Swakshyar Saumya Pal⁴, Rupak Roy⁴, Suganeswari Ganesan⁴, Tarun Sharma⁵

Abstract

Objective: The study assessed the four-year incidence of diabetic peripheral neuropathy (DPN) and the risk factors that can predict incident neuropathy in a south Indian population with type 2 diabetes.

Research Design and Methods: 1175 diabetic individuals were identified with known diabetes at baseline. At baseline, individuals underwent assessment of fasting plasma glucose and HbA₁c, levels, body mass index, waist-hip ratio, blood pressure, blood cholesterol and lipid levels, and ophthalmic evaluation including visual acuity, specular microscopy of the corneal endothelium, cataract grading and diabetic retinopathy assessment. Subjects were re-examined after four years for the assessment of incident neuropathy; 713 individuals were found eligible at follow-up. The presence of neuropathy was assessed at baseline and at follow-up and was defined as a Vibration Perception Threshold of ≥ 20 Volts.

Results: The four-year incidence of any neuropathy was 28.4%. Factors predictive of incident diabetic neuropathy were greater age at baseline (OR = 1.068), higher body mass index (OR = 1.034), presence of diabetic retinopathy (OR = 4.879) and lower socioeconomic status (OR = 4.841), when adjusted for several potential confounding factors.

Conclusions: The four-year incidence of diabetic neuropathy in a south Indian population with type 2 diabetes is 28% and can be predicted by ophthalmic and clinical variables. These factors may be utilized in the assessment, monitoring and intervention in individuals with diabetes in an effort to prevent or delay the development of diabetic peripheral neuropathy.

Introduction

Peripheral neuropathy is a devastating complication of diabetes with a very high prevalence of 30% to 50%.[1] Neuropathy remains the leading cause of non-traumatic foot ulceration and amputation, leading to decreased mobility, poor quality of life, falls, fractures, and even life-threatening consequences.[2] The crucial factor is that there is no effective treatment to date. India ranks the second highest in terms of rising prevalence of diabetes;[3] as a result, the microvascular and macrovascular complications are also expected to soar to higher proportions. Knowledge of the predisposing risk factors is thus paramount in order to facilitate early detection and prevention of avoidable complications. The current knowledge however, is limited to the prevalence of peripheral neuropathy. Therefore, our study sought to determine the incidence of neuropathy and its predictive risk factors in a south Indian population with diabetes. Subjects with type 2 diabetes were recruited at baseline were re-examined after four years and the incidence of peripheral neuropathy was assessed in relation to the baseline risk factors that may predict future development of neuropathy.

Methods and Materials

The study was approved by our Institutional Review Board, and was conducted in accordance with the Helsinki Declaration. Study subjects who provided written informed consent were recruited from the Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS). The study design and research methodology of SN-DREAMS-I is described in detail elsewhere.[3]

The study area was Chennai metropolis with a population of 4.3 million, distributed in 155 divisions of 10 zones. As a sample, a total of 5999 people from the general population aged >40 years were enumerated; multistage random sampling was stratified on the basis of economic criteria. Of the 5999 subjects enumerated, 1175 persons with a known history of diabetes defined per the World Health Organization (WHO),[4] were examined at baseline. A total of 713 subjects with gradable retinal photographs were eligible for the study. Figure 1 shows the number of participants at baseline and at follow-up.

Assessment of risk factors at baseline

Demographic and clinical variables such as age, gender, height, weight, resting blood pressure, socio-economic status (SES) duration of diabetes, smoking habits, family history of diabetes, neuropathy and nephropathy history (tingling, numbness, foot ulcers and amputated toe/foot) and diabetic treatment and urine albumin were recorded. The SES was stratified as low SES (score, 0-14), middle SES (score, 15-28) and high SES (score, 29-42).[3] A subject was considered normoalbuminuric if the albumin-creatinine ratio (ACR) was less than 30 mg/g, microalbuminuric if ACR
is between 30 and 300 mg/g and macroalbuminuric if ACR was above 300 mg/g.3 Patients were considered to be known diabetics, if they were using hypoglycemic drugs, either oral or insulin or both. Hypertension was defined as blood pressures >140/90 mm Hg or if the patients were using antihypertensive drugs.3

**Diabetic neuropathy assessment**

Diabetic neuropathy assessment was done by measuring Vibration Perception Threshold (VPT) using a sensiometer. The VPT was measured by a single observer by placing the biothesiometer probe perpendicular to the distal plantar surface of the great toe of both legs. The VPT was measured to assess the corneal endothelial status. Inc, Hyogo, Japan was performed to assess the corneal endothelial status. The centres of contiguous cells were marked, after which the computer automatically calculated and displayed the endothelial cell density (cells/mm2), coefficient of variation (CV) (%), and hexagonality (%), and analyzed the number of cells. The corneal endothelial cell density, hexagonality and the CV were analyzed.

**Visual acuity**

Visual acuity (VA) was estimated using the modified ETDRS chart (Light House Low Vision Products, New York, NY, USA) or Landolt’s ring test for those who could not read the English alphabet. Visual acuity in the better eye was considered for the assessment of visual impairment based on the WHO criteria. VA worse than 6/18 was defined as visual impairment.

**Corneal endothelium parameters**

Noncontact specular microscopy (Konan Noncon Robo Ca Sp 8000; Konan Inc, Hyogo, Japan) was performed to assess the corneal endothelial status. The centres of contiguous cells were marked, after which the computer automatically calculated and displayed the endothelial cell density (cells/mm²), coefficient of variation (CV) (%), and hexagonality (%), and analyzed the number of cells. The corneal endothelial cell density, hexagonality and the CV were analyzed.

**Table 1: Comparison of neuropathy status at baseline and 4-year follow up**

<table>
<thead>
<tr>
<th>Neurpathy status at baseline</th>
<th>No DPN</th>
<th>Mild DPN</th>
<th>Moderate DPN</th>
<th>Severe DPN</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neuropathy (No DPN)</td>
<td>422</td>
<td>82</td>
<td>75</td>
<td>11</td>
<td>590</td>
</tr>
<tr>
<td>Mild</td>
<td>17</td>
<td>10</td>
<td>13</td>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td>Moderate</td>
<td>22</td>
<td>14</td>
<td>15</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>Severe</td>
<td>7</td>
<td>3</td>
<td>15</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>Total</td>
<td>468</td>
<td>109</td>
<td>118</td>
<td>18</td>
<td>713</td>
</tr>
</tbody>
</table>

**Cataract evaluation**

Lens opacities were graded using the lens opacities classification system III (LOCS chart III, LeoT. Chylack, Harvard Medical School, Boston, MA); significant nuclear sclerosis was defined as nuclear opalescence of N2 or more.

**Diabetic retinopathy grading**

All patients had their fundi photographed by means of 45° four-field stereoscopic digital photography. The diagnosis of diabetic retinopathy was based on the modified Klein classification.6 For those who showed evidence of any retinopathy, additional 30° seven-field stereo digital pairs were taken. All photographs were graded by two independent ophthalmologists in a masked fashion; the grading agreement was high (κ = 0.83).

**Statistical analysis**

Statistical analyses were performed using the statistical software (SPSS for Windows, ver.17.0 SPSS Inc, Chicago, IL, USA). A chi-squared test was used to compare proportions amongst groups. Univariate and step-wise multiple logistic regression analyses were performed using presence or the absence of incident neuropathy as the dependent variable. A p value of <0.05 was considered statistically significant.

**Results**

Tables 1-2 present the number of patients at risk and those who developed peripheral neuropathy (DPN) after four years. The four-year incidence of any neuropathy was 28.4%
and the progression to any neuropathy was 13.0%. The incidences of mild DPN, moderate DPN and severe DPN were 13.8%, 12.7% and 1.0%, respectively. The progression from mild to moderate DPN was 26.1%, moderate to severe DPN was 1.9% and that from mild to severe DPN was 4.7%.

Table 3 provides a summary of the baseline risk factors assessed using univariate analysis. Those with incident neuropathy were significantly older, had prolonged duration of diabetes, higher HbA1c levels and body mass index, higher systolic BP, lower waist-hip ratio, and lower socioeconomic status. Those with microalbuminuria had a greater risk of incident neuropathy compared with those with normal albumin levels at baseline. Presence of visual impairment at baseline, higher LOCS scores were associated with higher risk of incident neuropathy on univariate analysis.

Table 4 provides a summary of the factors at baseline predictive of incident neuropathy assessed using logistic regression. Greater age (OR =1.068), higher BMI (OR =1.034), and the presence of DR (OR =4.879) and lower socioeconomic status (OR =4.841) were associated with incident neuropathy after four years when adjusted for variables that were significant on univariate analysis.

**Discussion**

The current study sought to determine the four-year incidence of neuropathy and its risk factors in a south Indian population with diabetes. The incidence of neuropathy assessed by VPT was seen in 28.4% of the subjects who did not have DPN at baseline, while, worsening of pre-existing DPN was observed in 13%. This suggests that roughly one in four individuals with diabetes is at risk of developing neuropathy. Greater age, lower socioeconomic score, higher body mass index and the presence of DR are risk factors for incident neuropathy, when adjusted for several potential confounding factors. The VPT predominantly tests for the function of large nerve fibres. An abnormal VPT has been shown to be associated with gangrene and foot ulceration. The reason that >80% of the morbidity in relation to distal symmetric peripheral neuropathy is associated with involvement of the large nerve fibres makes VPT a viable testing option.
We also observed higher BMI to be a risk factor for incident neuropathy. Few other studies report an association between peripheral neuropathy and BMI ≥ 30 kg/m². Subjects with neuropathy are reported to be heavier than those with no neuropathy and that obesity is associated with loss of small unmyelinated axons of intraepidermal nerve fibre density. Obesity or higher BMI could be associated with the mechanical pressure on the nerve in the lower extremities and therefore may accelerate the pathological process in the peripheral nerves. In addition, BMI represents modifiable risk factor. Another likely explanation could be pathophysiological mechanisms at the cellular level such as mitochondrial dysfunction, deposition of fat, protein glycation, and oxidative stress leading to chronic inflammatory process.

The strengths of our study is that it is a population-based study and a prospective longitudinal study that followed up a large cohort of subjects with type 2 diabetes. We assessed for the risk factors for incident neuropathy after taken into account, several potential clinical and ophthalmic confounders.

A limitation of our study is that the dropout rate was about 28%. As a result, the clinical characteristic in the drop outs is not known. In addition, a compromised vibration perception suggests the involvement of predominantly the long peripheral nerves and may well represent a sub-set of peripheral neuropathy. Utilization of techniques that examine sensory attributes such as mild touch/pressure/ pin-prick and hot/cold sensation may be valuable and may exhibit variation in the predictive risk factors.

In conclusion, the four-year incidence of diabetic peripheral neuropathy is 28%. Factors predictive of future neuropathy are greater socioeconomic status and the presence of diabetic retinopathy. These factors may be utilized for further evaluation, monitoring and intervention in an effort to prevent or delay the development of peripheral neuropathy in diabetic patients.

References
Physicians Perception of Rheumatology Practice and Training in India

Durga Prasanna Misra1, Vinod Ravindran2, Aman Sharma3, Anupam Wakhlu4, Vir Singh Negi5, Ved Chaturvedi6, Vikas Agarwal7*

Abstract

Objective: To assess physicians' perception and their felt competence in dealing with patients with rheumatic complaints.

Methods: We assessed the quantum of rheumatological disorders seen by physicians in India, their felt competency in dealing with such patients, and their perceived adequacy of undergraduate and postgraduate medical training in Rheumatology by means of an anonymized questionnaire conducted at the annual national conference of internal medicine specialists.

Results: Our analysis of 333 respondents revealed that while they saw an average of 10 patients with rheumatic complaints every month, the felt competence in dealing with such cases was only a median of 6/10 (interquartile range 5-7). About 75% professed little or no exposure to Rheumatology as undergraduates, whereas only 20% perceived adequacy of training during internal medicine residency to treat such diseases confidently. 78.37% and 67.7% perceived an inadequacy of rheumatology training at undergraduate and postgraduate level respectively, and 83% felt the need for further training or sensitization in Rheumatology.

Conclusion: There remains an unmet need to enhance existing undergraduate and postgraduate internal medicine curricula in India to impart greater skills in the diagnosis and management of rheumatic diseases. Initiatives and government funding to establish short-term training courses in Rheumatology for established internal medicine faculty, to enable them to provide basic Rheumatology services at their respective hospitals, are urgently needed.

Introduction

India is home to nearly a fifth of the world’s population.1 The system of modern medical education in India has its roots in the colonial days of British rule, wherein the basic undergraduate MBBS degree (Bachelor of Medicine and Bachelor of Surgery) can be followed by postgraduate degrees (MD, MS, DNB), which can then further be followed by subspecialty training to obtain DM (Doctor of Medicine) degrees for medical specialities, MCh (Magister Chirurgiae) degrees for surgical specialities, or certification by the DNB for super specialities (DNB super specialty).2 In India, the specialty of Rheumatology is now universally recognized as Clinical Immunology and Rheumatology.3 For the purpose of the present paper, we shall use the term Rheumatology for consistency.

While there is a scarcity of epidemiologic studies on rheumatic diseases from India, estimates suggest that nearly 15-20% of the population suffer from rheumatic diseases.4 A recently published analysis from the global burden of disease study revealed that low back and neck pain, and musculoskeletal complaints are amongst the top twenty causes of disability adjusted life years (DALYs) in India.5 Rheumatology is an upcoming sub-specialty in India, and there is a scarcity of experts for the management of rheumatic diseases in India.6 Therefore, most patients with rheumatic diseases are dealt with by doctors with either a basic undergraduate MBBS degree or a postgraduate degree in Internal Medicine or Orthopaedic surgeons. Considering the prevalence of rheumatic diseases in the community, it is imperative that present-day undergraduate and basic postgraduate medical curricula should impart adequate basic competence in Rheumatology. To assess whether this is indeed the case, we undertook a survey of practicing physicians to assess the quantum of rheumatic diseases seen by them, their confidence in dealing with patients with rheumatic complaints, their perceptions of the adequacy of present day undergraduate and postgraduate medical rheumatology training, as well as their learning after obtaining postgraduate degrees via means of conferences and lectures in rheumatology. Obtaining such information would enable suitable modification of existing courses to enable general physicians to better manage rheumatic diseases in India.

Methods

A questionnaire was designed to assess the practice and training of physicians in Rheumatology. This questionnaire was formulated by discussion amongst the authors to include questions that would help

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Received: 27.06.2018; Revised: 31.10.2018; Accepted: 24.04.2019
assess the amount of rheumatic diseases they see in their daily practice, the felt competence of physicians in dealing with such patients and their perceived adequacy of training under undergraduate and postgraduate medical training. The questionnaire included basic demographic information (type of practice setting, last formal degree and number of years in practice), while not seeking personal details such as name, age, gender or place where they practice, so as to preserve anonymity of the participating physicians. Since physicians are allowed to concomitantly have private rooms in government as well as private setups in some parts of India, multiple responses were allowed for a single respondent for the question related to the setting of practice. Further, the number of patients with rheumatic diseases seen on an average every month, the confidence of the treating physician in dealing with such cases on a scale of 0-10, the quantum of rheumatology exposed to at undergraduate and postgraduate levels, whether there was a felt deficit in the existing undergraduate and postgraduate curricula with respect to rheumatology, and whether the physician felt a need for further training at these levels or a requirement for greater sensitization to or training in this subject were assessed.

### Table 1: Demographics of respondents

<table>
<thead>
<tr>
<th>Question / Option</th>
<th>n</th>
<th>%</th>
<th>Total responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practice setting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic - Government</td>
<td>135</td>
<td>40.54</td>
<td>333</td>
</tr>
<tr>
<td>Academic - Private</td>
<td>113</td>
<td>33.93</td>
<td></td>
</tr>
<tr>
<td>Private practice – Corporate hospital</td>
<td>44</td>
<td>13.21</td>
<td></td>
</tr>
<tr>
<td>Private practice – self - Urban</td>
<td>50</td>
<td>15.01</td>
<td></td>
</tr>
<tr>
<td>Private practice – self - Rural</td>
<td>33</td>
<td>9.9</td>
<td></td>
</tr>
<tr>
<td>Last formal qualification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MBBS</td>
<td>66</td>
<td>19.82</td>
<td>333</td>
</tr>
<tr>
<td>MD/DNB (Broad specialty)</td>
<td>249</td>
<td>74.77</td>
<td></td>
</tr>
<tr>
<td>DM/DNB (Super specialty)</td>
<td>18</td>
<td>5.41</td>
<td></td>
</tr>
<tr>
<td>Number of years in practice</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-5</td>
<td>115</td>
<td>43.39</td>
<td>265 (79.58%)</td>
</tr>
<tr>
<td>5-15</td>
<td>61</td>
<td>23.01</td>
<td>129</td>
</tr>
<tr>
<td>15-25</td>
<td>52</td>
<td>19.62</td>
<td>105</td>
</tr>
<tr>
<td>&gt;25</td>
<td>37</td>
<td>13.96</td>
<td>74</td>
</tr>
</tbody>
</table>

### Supplementary Table 1: Rheumatology practice and training in India Questionnaire

1. In which setting do you practice? (Please TICK as many as applicable)
   - Academic –government
   - Academic – private
   - Private practice – Corporate
   - Private practice – Self
   - predominantly urban
   - predominantly rural

2. What was your last formal degree? (Please TICK)
   - MBBS
   - MD/ DNB (broad-specialty)
   - DM/ DNB (super-specialty)

3. For the question related to the setting of practice, please specify:
   - Academic – private
   - Academic – government
   - Corporate hospital
   - Urban
   - Rural

4. How many years after finishing postgraduation have you been practicing for? (Please CIRCLE)
   - 1-5 Yrs.
   - 5-15 Yrs.
   - 15-25 Yrs.
   - >25 Yrs.

5. Approximately how many patients with rheumatic diseases do you see in a month?

6. How confident do you feel in managing patients with rheumatic diseases? Please rate on a scale of 0 to 10 (0 – not at all confident, 10 – fully confident) (Please CIRCLE)
   - Not at all confident
   - Somewhat confident
   - Absolutely confident

7. How much Rheumatology were you exposed to as an undergraduate? (Please TICK)
   - None
   - Minimal
   - Enough to distinguish different diseases
   - Enough to treat confidently

8. How much Rheumatology were you exposed to as a postgraduate trainee [MD/ DNB (broad-specialty)]? (Please TICK)
   - None
   - Minimal
   - Enough to distinguish different diseases
   - Enough to treat confidently

9. Do you feel that in today’s training curriculum, there is a lacuna/ deficit in rheumatology training?
   a. At undergraduate training level (Please CIRCLE)
   b. At postgraduate training level (MD/ DNB (broad-specialty)) (Please CIRCLE)

10. Do you feel a need to discuss with a rheumatologist while treating a patient with rheumatological disease? (Please CIRCLE)
   - Yes
   - No
   - Cannot comment

11. Do you feel there is a need to have more Rheumatology training at UG/PG level?
   a. at UG level? (Please CIRCLE)
   b. at PG level? (Please CIRCLE)

12. Do you feel there is a need to have sensitization/training in rheumatology? (Please TICK)
   - No need
   - May be helpful
   - Will be definitely helpful
   - Is an unmet need and must be undertaken

13. Do you think regular CME/ workshops focused on Rheumatology as a whole would help your practice of rheumatology? (Please CIRCLE)
    - Yes
    - No

14. Do you think regular CME/ workshops focused on specific rheumatic diseases would help your practice of Rheumatology? (Please CIRCLE)
    - Yes
    - No

15. Which (or when) was the last rheumatology lecture you attended before APICON 2018?

16. Have you had the opportunity to attend any rheumatology CME or IRACON (Rheumatology national conference) (Please CIRCLE)

17. Do you feel that there is a scarcity of investigational facilities available for rheumatic diseases in the place where you practice? (Please CIRCLE)
Also, the usefulness of conferences or continuing medical education (CME) programs focused on rheumatology, as well as whether the physicians had attended rheumatology lectures or conferences in the past were assessed. The complete set of questions included in the questionnaire is available in supplementary Table 1.

Physicians attending the national conference of internal medicine specialists (Association of Physicians of India Conference – APICON) in 2018 were provided this anonymized questionnaire. Responses were collated and analyzed using Statistical Package for Social Sciences (SPSS) version 16 and GraphPad Prism (version 6.00, Mac OS X, GraphPad Software, La Jolla, California, USA). Since this was an anonymized survey of educational practices, exemption from ethical committee review was obtained from the Institute Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow [IEC CODE – 2018-62-IP-EXP] as per the regulations of the Indian Council for Medical Research (ICMR). For analysis, the questions related to type of practice setting, last formal qualification, number of patients with rheumatic diseases seen every month and the degree of confidence in dealing with such patients were taken as the minimum required to be answered to pass quality control. The data collected was analyzed using descriptive statistics (number and percentage) to assess the number of responses to each option in the questionnaire.

### Results

There were a total of 392 responses, of which 333 (84.95%) passed quality control. Further results are presented based on these 333 responses. Most of the questions had response rates in excess of 80%, except those related to duration of practice (Supplementary table 1, question 3 – 79.58%) and the question related to whether there is a need to have more training in Rheumatology at undergraduate level (Supplementary Table 1, question 11a – 75.67%).

The demographic details are presented in Table 1. Of these, a majority practiced in either an academic government setup (40.54%) or an academic private setup (33.93%). About four-fifths of the respondents had acquired a postgraduate degree, most of which were basic postgraduate degree holders (MD or DNB Broad specialty – 74.77%). The respondents were spread out with respect to duration of practice, with a majority being in practice for 1-5 years. The physicians attended to a median of 10 patients with rheumatic diseases every month (interquartile range – IQR – 5-20). On a scale of 0 to 10, the median degree of confidence in managing such patients was 6 (IQR 5-7).

The results of questions related to the exposure to Rheumatology during undergraduate and postgraduate medical studies are summarized in Table 2. Most of the physicians felt they had learnt a major chunk of their Rheumatology practice at the postgraduate level or after completing basic postgraduate training. Nearly three-fourth professed that they had little or no exposure to Rheumatology as undergraduate medical students. Whereas 56.17% rated their exposure to Rheumatology at a basic postgraduate level as adequate to distinguish different rheumatic diseases, only 20.06% professed adequate exposure to treat different rheumatic diseases confidently. Nearly four-fifth of respondents felt there was a deficit in rheumatology training in undergraduate curriculum, whereas, about two-thirds perceived a similar deficit in the prevalent postgraduate medical curriculum. Most respondents (96.32%) felt a need for a greater quantum of Rheumatology training at postgraduate level, whereas, 79% felt a similar need at the undergraduate level.

Greater than 99% of respondent physicians professed that there is a need for sensitization towards or additional training in Rheumatology, with a majority (61.9%) feeling that this would be definitely helpful, and 21.27% agreeing that this was an unmet need in the present day scenario. While nearly 87% felt a need to discuss with a Rheumatologist while treating a patient with rheumatic complaints, only 69.62% said they had access to such a rheumatologist. More than 95% respondents felt that regular CME programs focusing either on Rheumatology as a whole or on specific rheumatic diseases were useful in enhancing their practice of Rheumatology. However, greater than two-thirds professed to not having attended any rheumatology CME or the national rheumatology conference. The majority (77.5%) felt that there was a scarcity of investigational facilities for the rheumatic diseases.

We also analyzed the responses to the queries related to adequacy of Rheumatology training. Approximately 75% of respondents felt that there was a need for more Rheumatology training at both undergraduate and postgraduate levels. Whereas 79.37% of undergraduates felt a need for a greater quantum of Rheumatology training at UG level, 96.32% (UG) and 87.39% (PG) of postgraduates felt a need for more Rheumatology training at PG level. Furthermore, 20.06% found their exposure to Rheumatology at the PG level as adequate to distinguish different rheumatic diseases, whereas, only 74.26% rated their exposure at UG level as adequate.

### Table 2: Exposure to Rheumatology during undergraduate and postgraduate medical training

<table>
<thead>
<tr>
<th>Question / Option</th>
<th>n</th>
<th>%</th>
<th>Total responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>The quantum of Rheumatology that you practice, when do you feel you learnt it the most?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- At the UG training level</td>
<td>32</td>
<td>9.78%</td>
<td>327 (98.2%)</td>
</tr>
<tr>
<td>- At the PG training level</td>
<td>218</td>
<td>66.66%</td>
<td></td>
</tr>
<tr>
<td>- After completing basic postgraduate training</td>
<td>77</td>
<td>23.54%</td>
<td></td>
</tr>
<tr>
<td>How much Rheumatology were you exposed to as an undergraduate or postgraduate?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UG?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- None</td>
<td>36</td>
<td>10.88%</td>
<td>5 1.54</td>
</tr>
<tr>
<td>- Minimal</td>
<td>212</td>
<td>64.05%</td>
<td>72 22.22</td>
</tr>
<tr>
<td>- Enough to distinguish different diseases</td>
<td>74</td>
<td>22.36%</td>
<td>182 56.17</td>
</tr>
<tr>
<td>- Enough to treat confidently</td>
<td>9</td>
<td>2.72%</td>
<td>65 20.06</td>
</tr>
</tbody>
</table>

Do you feel that in today’s training curriculum, there is a lacuna/deficit in Rheumatology training? at UG level? at PG level?

<table>
<thead>
<tr>
<th>n</th>
<th>%</th>
<th>Total responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>221</td>
<td>78.37%</td>
</tr>
<tr>
<td>No</td>
<td>44</td>
<td>15.60%</td>
</tr>
<tr>
<td>Cannot comment</td>
<td>17</td>
<td>6.03%</td>
</tr>
</tbody>
</table>

Do you feel there is a need to have more Rheumatology training at UG/PG level?

<table>
<thead>
<tr>
<th>n</th>
<th>%</th>
<th>Total responses</th>
</tr>
</thead>
<tbody>
<tr>
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<td>221</td>
<td>78.37%</td>
</tr>
<tr>
<td>No</td>
<td>44</td>
<td>15.60%</td>
</tr>
<tr>
<td>Cannot comment</td>
<td>17</td>
<td>6.03%</td>
</tr>
</tbody>
</table>

PG – Postgraduate, UG - Undergraduate
training in undergraduate and postgraduate curricula, need for further Rheumatology training and strategies to enable continuing rheumatology training among physicians, including access to practicing Rheumatologists, as well as availability of investigation facilities for rheumatic diseases including the responses from the 59 questionnaires that had failed quality control (a total of 392 responses). This data was similar to that presented in Table 2 and in the results (data not shown).

Discussion

Our survey of more than three hundred physicians revealed that, while they encountered a significant number of patients with rheumatic complaints in their practice, there was a lack of confidence in dealing with such patients. A majority confessed a lack of adequate training to manage such conditions. While they encountered a significant number of patients with rheumatic complaints, the majority of respondents felt that there was a lacuna in training in Rheumatology at the undergraduate level as well as the postgraduate level. Since deficits in undergraduate curricula and lack of competence in rheumatology amongst postgraduate residents in internal medicine have been also reported from other parts of the world. However, the lack of available Rheumatologists in this part of the world further magnifies this problem. In this context, it is reasonable to suggest that the medical curriculum in India should be redesigned with a greater emphasis on imparting competence in Rheumatology at both the undergraduate and postgraduate levels. Such a curriculum should be designed such that undergraduate medical doctors can accurately diagnose different rheumatic diseases, being able to distinguish major categories of rheumatic diseases (inflammatory arthritis from non-inflammatory joint pains or soft tissue rheumatism; systemic inflammatory diseases such as lupus and vasculitis). They should also be aware of the medical management of such rheumatic diseases, and undergraduate training should ensure competency in basic and basic rheumatological procedures such as joint arthrocentesis. The postgraduate internal medicine curriculum should ensure adequate exposure to rheumatic diseases, with physicians being trained such that they can accurately distinguish different rheumatic diseases, manage common conditions such as rheumatoid arthritis, osteoarthritis, and gout, while referring more complex patients to a specialist, and ensuring early referral of complicated systemic rheumatic diseases such as lupus or vasculitis to a tertiary care center well equipped to deal with them. The ability to diagnose and manage common rheumatic diseases should also be mandatorily tested in the postgraduate internal medicine exit exam, as is already done with cases representing other major specialties such as Cardiology, Neurology and Pulmonary Medicine.

The actual number of patients with rheumatic complaints seen in the OPD is also increasing with time (Figure 1). This might be due to the gradual increase in population of the country, as well as increasing awareness about rheumatic diseases in the community. In this context, it is reasonable to suggest that the medical curriculum in India should be redesigned with a greater emphasis on imparting competence in Rheumatology at both the undergraduate and postgraduate levels. Such a curriculum should be designed such that undergraduate medical doctors can accurately diagnose different rheumatic diseases, being able to distinguish major categories of rheumatic diseases (inflammatory arthritis from non-inflammatory joint pains or soft tissue rheumatism; systemic inflammatory diseases such as lupus and vasculitis). They should also be aware of the medical management of such rheumatic diseases, and undergraduate training should ensure competency in basic and basic rheumatological procedures such as joint arthrocentesis. The postgraduate internal medicine curriculum should ensure adequate exposure to rheumatic diseases, with physicians being trained such that they can accurately distinguish different rheumatic diseases, manage common conditions such as rheumatoid arthritis, osteoarthritis, and gout, while referring more complex patients to a specialist, and ensuring early referral of complicated systemic rheumatic diseases such as lupus or vasculitis to a tertiary care center well equipped to deal with them. The ability to diagnose and manage common rheumatic diseases should also be mandatorily tested in the postgraduate internal medicine exit exam, as is already done with cases representing other major specialties such as Cardiology, Neurology and Pulmonary Medicine.

Literature also suggests that even newly-opened Rheumatology services in India become very busy over a short period of time, emphasizing the need for more physicians capable of treating rheumatic diseases in the country. Furthermore, specialist nurses and trained paramedical staff are generally not available in the prevalent system of medicine practiced in India, quite unlike established services in Europe and elsewhere, where such healthcare personnel share a significant burden of the patient management along with the doctors. Hence, the actual burden of patient care encountered by a practicing rheumatologist in India is much more than that reflected by the numbers of patients alone. In the opinion of the authors, there is an unmet need to establish Rheumatology clinics at each and every tertiary care medical college, whether government funded or private, in India. Since around thirty specialists are trained every year in the existing situation, there remains an urgent need to increase the number of formal Rheumatology DM or DNB courses in India. An ancillary strategy could be to introduce short-term courses (ranging from 3 months to one year) for internal medicine specialists already working in medical colleges and district hospitals, at the centers where training facilities for Rheumatology already exist. Further, such physicians who are thereby trained should be encouraged to open Rheumatology clinics in their respective medical colleges.

National healthcare programs have been established by the government of India which provide a framework and
infrastructure right up to the level of the community for the management of diseases with higher prevalence. While there are existing national programs for diseases such as mental health illnesses,\textsuperscript{21} these ranked below rheumatic and musculoskeletal diseases in terms of DALYs in a recently published analysis from the global burden of diseases study from India.\textsuperscript{8} Currently, no national programs exist for the management of rheumatic diseases in India. The government should initiate planning and invest resources to further Rheumatology care in India. As a starting point, they could incentivize physicians by providing them funding to train in such short-term programs, as well as possibly provide an additional financial benefit should they succeed in opening such Rheumatology clinics. There are greater than 16000 internal medicine specialists in India currently.\textsuperscript{22} Even if every third physician could be motivated to provide basic rheumatology services in addition to their existing services, this would enable significantly greater availability of services for the management of rheumatic diseases all over the country.

Greater than three-fourth of our respondents felt that CME programs

<table>
<thead>
<tr>
<th>Table 3: Suggestions for enhancement of rheumatology services in India</th>
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<tbody>
<tr>
<td>1. Redesign undergraduate medical curriculum – mandate the ability to accurately diagnose different rheumatic diseases.</td>
</tr>
<tr>
<td>2. Reframe postgraduate medical curriculum – impart competence in joint examination, knowledge regarding management of all rheumatic diseases including mandatory competence assessment regarding management of common rheumatic diseases such as rheumatoid arthritis, osteoarthritis, gout and soft tissue rheumatism.</td>
</tr>
<tr>
<td>3. Increase the number of formal three-year super specialty courses in Rheumatology by at least five to ten fold from the presently available number.\textsuperscript{2}</td>
</tr>
<tr>
<td>4. Introduce additional structured short-term training courses (3 month to 1 year in duration) for internal medicine specialists working in medical colleges or district hospitals to impart basic skills to diagnose rheumatic diseases, treat common rheumatic diseases and refer more complicated patients or rarer rheumatic diseases such as vasculitis or lupus to a Rheumatologist at the earliest.</td>
</tr>
<tr>
<td>5. Government funding and encouragement for such short term training programs in Rheumatology and incentivize hitherto trained individuals to open Rheumatology clinics in Internal Medicine departments all over the country.</td>
</tr>
<tr>
<td>6. Government/national society funding of single-day continuing medical education programs in every medical college at least annually.</td>
</tr>
<tr>
<td>7. Establishment of national goals and policies to fund community Rheumatology services, akin to those already existent for non-communicable diseases like mental health and geriatrics.\textsuperscript{21}</td>
</tr>
<tr>
<td>8. Establishment of dedicated training programs for specialist nurses and physiotherapists with an emphasis on Rheumatology.</td>
</tr>
</tbody>
</table>

Table 3: Suggestions for enhancement of rheumatology services in India

undergraduate and postgraduate medical curricula to address this knowledge deficit, while providing short-term training courses to physicians to enable them to offer basic services for rheumatic diseases at the community level. It is the intention of the authors to design such short-term training courses for practicing internists after analyzing their perceptions and expectations of such training courses by means of in-depth questionnaires in a subsequent survey, which is already being designed. We also hope that the findings of the present survey shall provide an evidence base to enable changes in healthcare policies at the national level to enhance basic training, and, thereby, the greater availability of Rheumatology services in India. This could further serve as a model for establishing and improving Rheumatology services in other similarly economically challenged regions of the world such as neighbouring countries in South East Asia and Africa.\textsuperscript{12–14}

Abbreviations

APICON - Association of Physicians of India Conference; CME - continuing medical education; DALY - disability adjusted life years; DNB - Diplomate of the National Board of Examinations; DM - Doctor of Medicine (Super specialty); ICMR - Indian Council for Medical Research; IRA - Indian Rheumatology Association; IQR - Interquartile range; JIPMER - Jawaharlal Institute of Postgraduate Medical Education and Research; MBBS - Bachelor of Medicine and Bachelor of Surgery; MCh - Magister Chirurgiae; MD - Doctor of Medicine (Broad specialty); MS - Doctor of Surgery; OPD - out-patient department; PGIMER - Postgraduate Institute of Medical Education and Research; SGPGIMS - Sanjay Gandhi Postgraduate Institute of Medical Sciences; SPSS - Statistical Package for Social Sciences

References

Study of APOE Gene and D2S439 Marker in Patients of Rheumatoid Arthritis and their Correlation with Severity of Disease: A Case Control Study

LA Gauri*, Ummed Singh2, Suman Kapur3, Qadir Fatima4, Bhanwar Ranwa5, Aism Khan6, Ambreen Liyakat7, Rohitash Kularia8, Nisha9

Abstract

Aim: To delineate the genetic differences in polymorphism of the APOE and D2S439 marker genes for patients with and without rheumatoid arthritis and to study the distribution frequency of the prevalent alleles of these genes in clinically defined sub groups of patients/controls of Indian origin, specifically and their correlation with severity of disease using DAS score.

Material and Methods: This is a case control study where peripheral blood samples 160 cases and 150 controls were collected.

Results: We evaluated the association of the tetra nucleotide repeat microsatellite marker D2S439 lying at 231.27 cm position on the q arm of chromosome-2. The alleles of this marker ranged in size from 163bp-203bp in PCR product length corresponding to 5-15 (CTAT)n tetra repeats. The allele frequencies for this marker in the North Indian population are different from the CEPH populations. The longer alleles, >199bp (=14 or 15 CTAT repeats) were not observed. The genotypes after bimodal distribution differ significantly among cases and controls (p=0.003). Statistically significant difference was seen between cases and controls for ≥(CTAT)10 longer allele which was more prevalent in the adult RA cases than in controls. Severity of RA was defined by a DAS28 score of >6 on a scale of ten. No significant association was seen with the APOE polymorphism and disease severity.

Conclusion: The long allele of D2S439 marker representing an expansion of the CTAT, tetraterucleotide repeat doubles an individual’s the risk for developing RA.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that principally attacks the joints producing a inflammatory synovitis that often progresses to destruction of the articular cartilage and ankylosis of the joints.1 Rheumatoid arthritis can also produce diffuse inflammation in the lungs, pericardium, pleura, and sciera, and also nodular lesions, most common in subcutaneous tissue under the skin. Although the cause of rheumatoid arthritis is unknown, autoimmunity plays a pivotal role in its chronicity and progression.2

The incidence of RA is 3 cases per 10,000 populations per annum with M:F =1:3-5.3 First degree relative’s prevalence rate is 2-3% and disease genetic concordance in monozygotic twins is approximately 15-20%.4

Disease Susceptibility Genes

RA is strongly associated with Major
Patients with RA and extra-articular organ involvement have extensive T-cell abnormalities. HLA-C alleles and killer-like immunoglobulin-like receptor gene variants with suggested regulatory functions for immunosenescent T cells in extra-articular RA, have been shown to be associated with vasculitis in patients with RA.

The tumor necrosis factor (TNF) has been shown to be important in the pathogenesis of RA. A number of biallelic SNPs and 5 microsatellite markers in the TNF region have been identified. Interactions between the markers TNFa672 and TNFa1173 and SE genotypes have been reported to be associated with radiographic damage and disability. The TNFa6-SE interaction may also predict the development of rheumatoid nodules. Polymorphisms in other cytokine genes, such as interleukin (IL) 4 and IL-1β, IL-1α, and IL-1 receptor antagonist, may also affect radiographic progression and other outcomes.

The APOE gene, APOE, is mapped to chromosome 19 in a cluster with Apolipoprotein C2 and Apolipoprotein C2.APOE consists of four exons and three introns, totaling 3597 base pairs. The gene is polymorphic, with three major alleles APOE2, APOE3, APOE4, which translate into three isoforms of the protein: Normal-APOE-83, dysfunctional-APOE-s2 and APOE-e4.

It has been linked with chronic inflammatory diseases like DM-2, CHD, CVA and autoimmune diseases (i.e. RA).

D2S439 chromosome locus is also known as: G00-228-912, D2S439.202, GATA6E08, G00-686-802, and CHLC. GATA6E08.202.

Material and Methods

It was a case control study wherein all available patients and volunteers (only for blood samples) were recruited. Peripheral blood samples of 160 patients with age and sex matched 150 controls were collected at Rheumatology clinic and Medicine Department of S.P. Medical College, Bikaner after explaining the objective of the study and taking an informed consent from the patients or from guardian family members. All patients of rheumatoid arthritis above 16 years of age diagnosed as per American College of Rheumatology (ACR) criteria 1987 were included in the study.

Exclusion Criteria

1. All seriously ill patients of rheumatoid arthritis with associated illnesses like malignancy, renal failure, liver failure were excluded from this study.

2. Patients of RA with other connective tissue disorders like scleroderma, SLE, poliomyelitis etc (overlap syndrome) were excluded from this study.

Health Criteria: Not applicable in the present study. Only OPD/IPD patients were recruited and lactating mothers not recruited.

Procedure for conducting the study: The controls and the patients were explained about the purpose of the research study by the resident and who subsequently obtained a written consent from the recruited patients/controls. A detailed proforma was used to gather clinical history of the patients and information about the family history of the patient.

Blood Sampling Procedure

As explained above a proforma was used to gather clinical history of the patients/controls. Venous blood sample was drawn by skilled technical staff/nurse/doctor on the project, before the discharge of the patient with sterile disposable syringes and was immediately transformed to pre-labeled blood collecting vials containing 0.5M EDTA as anticoagulant and transported in ice from place of collection to lab.

The collected sample in the lab was centrifuged for 8 min. at 2000 RPM and serum was separated from sample in a plain vial and both were stored at -20°C till transport to genetic lab.

Table 1: Allelic frequency distribution of D2S439 Microsatellite marker repeats in cases of Rheumatoid Arthritis and control population

<table>
<thead>
<tr>
<th>Allele Frequency N(%)</th>
<th>PCR Product Size</th>
<th>Number of repeats</th>
<th>Cases N=160</th>
<th>Controls N=89</th>
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<tbody>
<tr>
<td>163</td>
<td>5</td>
<td>1</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>167</td>
<td>2</td>
<td>4 (1)</td>
<td>5 (3)</td>
<td></td>
</tr>
<tr>
<td>171</td>
<td>3</td>
<td>3 (1)</td>
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<td>175</td>
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<td>199</td>
<td>14</td>
<td>10 (45)</td>
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<tr>
<td>203</td>
<td>15</td>
<td>11 (21)</td>
<td>9 (6)</td>
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</table>

1(OR=0.089, 95% CI=0.03-0.26, p<0.0001); 2(OR=2.17, 95% CI=1.28-3.67, p=0.003); 3(OR=1.69, 95% CI=1.13-2.54, p=0.01)
UV spectroscopy and qualified on 0.8% agarose.

PCR Standardization: This DNA was used for allele specific PCR amplification of the selected genes on a Thermal Cycler using known primes. Amplified sequences of selected genes were analyzed for specific allele type present using RFLP, LP, SSCP, or DNA sequencing methods.

SNP analysis by RFLP/SSLP: RFLP’s (restriction fragment length polymorphisms) was typed by analysis of PCR product obtained from the amplification of target sequence on Thermal Cycler using known primers. Variation/s were characterized by polyacrylamide gel electrophoresis. DNA sequencing, was done using commercial source available.

Statistical Analysis: Appropriate statistical analysis was applied as and when required using Statistical software (SPSS version 10.0).

Results

Cases comprised of 115 females (Mean age 42.08±12.13 yrs) and 45 (mean age 48.4±12.8 years) males. The control group comprised of 150 unrelated healthy controls. The controls were deliberately chosen from higher age group to minimize the chances of errors in segregation of groups due to late onset of disease. Table 1 shows the clinical profile of the cases and the control group. The cases and controls did not differ significantly for any of the clinical parameters.

Mean age in cases was 44.35±13.79 years while in unrelated controls it was 51.20±17.2 years. Systolic BP was 130.65±9.71 and 129.32±10.11 in cases and unrelated controls respectively. While TC, TG, urea, Total Protein, Albumin, Globulin, A/G ratio and creatinine was not done in unrelated controls subjects.

Genetic analysis of cases and controls for allelic frequency distribution of D2S439 Microsatellite marker repeats revealed maximum number of cases in 191 PCR product size i.e. 118 in cases while in controls it was also in PCR product size 191 i.e. 46. Least number of cases were from 163 where not a single case was found (Table 1).

The north Indian population, specifically from western Rajasthan differs from the Caucasian population in distribution of various alleles of the D2S439 marker.
Table 3: Genotypic and allelic distribution of APOE in the groups studied

<table>
<thead>
<tr>
<th>Category</th>
<th>APOE Genotype</th>
<th>APOE alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>N (0.00)</td>
<td>E2-2 (0.07) E3-3 (0.70) E4-4 (0.02) 2N (0.05) E2-4 (0.83) E3-4 (0.11)</td>
</tr>
<tr>
<td></td>
<td>(179)</td>
<td>(13 127 3) (31 4 358) (18 298 42)</td>
</tr>
<tr>
<td>Controls</td>
<td>(149)</td>
<td>(0.00) 4 1 98 41 298 8 242 50</td>
</tr>
<tr>
<td></td>
<td>(0.02) 0.0 (0.00) 0.65 (0.28) 0.0 (0.02) 0.0 (0.01)</td>
<td></td>
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</tbody>
</table>

Table 4: Genotypic and allelic frequencies of the APOE gene in cases controlled for DAS score

<table>
<thead>
<tr>
<th>DAS28&lt;6 (n=86)</th>
<th>E2-2 (0.11) E2-3 (0.00) E2-4 (0.00) E3-3 (0.71) E3-4 (0.07) E4-4 (0.81)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(0)</td>
</tr>
<tr>
<td></td>
<td>(9)</td>
</tr>
<tr>
<td></td>
<td>(13)</td>
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<tr>
<td></td>
<td>(141)</td>
</tr>
<tr>
<td></td>
<td>(18)</td>
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<tr>
<td></td>
<td>(0.02)</td>
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<tr>
<td></td>
<td>(0.00)</td>
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<tr>
<td></td>
<td>(0.71)</td>
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<td>(0.02)</td>
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<td>(0.10)</td>
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</table>

Discussion

Almost 67% of the cases comprised of females while only 33% cases were males. The number of nicotine users among cases was only 11% while nonsmokers and nonalcoholic comprised 89% of subjects. This also could be attributed to the fact that 67% of the cases were females. A similar trend was observed for use of alcohol also. On comparing the socioeconomic status most of our cases being females fall into the category of housewives (66%) while the remaining 24% population was either farmers or self employed individuals. The pattern of the recruited group mainly showed a vegetarian profile (68%) with only 32% individuals being non-vegetarian. The case cohort was analyzed for the presence of rheumatoid nodules and a very small number of cases (3%) were found to have nodules. On further evaluation of the cases for joint deformity nearly 59% cases showed joint deformity.

Cases were evaluated for duration of illness and a positive correlation (R²=0.08 p<0.001), was seen with the disease score. This shows that as the duration of the disease increases the severity of the disease among cases also increases considerably (Figure 1). In fact the duration of the disease also seem to increase the systolic blood pressure among the individuals, which means that as the duration and the severity of the disease increases, the tendency for elevated SBP increases and hence the risk for CVD increases.

D2S439 Polymorphism in Rheumatoid Arthritis

In the course of this study we evaluated the association of the tetra nucleotide repeat microsatellite marker D2S439 lying at 231.27cM position on the q arm of chromosome 2. The alleles of this marker ranged in size from 163bp to 203bp in PCR product length corresponding to 5-15 (CTAT) repeat in tetra repeats. Population data has shown that this marker is a highly polymorphic marker with a hetrozygosity and polymorphic information content (PIC value) of more than 0.80. The distribution of the allele frequency for this STR marker among the studied cases (160) and controls (89) is shown in the Table 2 and Figure 2.

On comparison with the world frequency of this marker it was seen that the allele frequencies for this marker in the north Indian population are different from the CEPH populations (Utah Residents with north and western European ancestry). The longer alleles, >199bp (=14 or 15 CTAT repeats) were not observed in this population as shown in Figure 3.

The cohort was further analyzed for differences in the distribution of various alleles of this marker. The distribution of the allele and genotypic frequency is described in Table 2 and Figure 2. The alleles showing significant difference in the cases and controls are marked. The population was in HWE in controls (p>0.05). Significant difference in the allele frequency was seen in alleles 6 (OR=0.089, 95% CI=0.03-0.26, p<0.0001), showing significant protection for RA and 7 (OR=2.17, 95% CI=1.28-3.67, p=0.003), and 8 (OR=1.69, 95% CI=1.13-2.54, p=0.01) both imparting a two-fold risk for developing rheumatoid arthritis.

The allele frequencies of the significant alleles 6, 7 and 8 constituted almost 60% of the overall allele frequency reported for cases of RA where as in controls they contributed to only 49% of the overall allele frequency. On further analysis the cohort was divided into two groups based on the natural tendency for the bimodal distribution (Table 3). The distribution was based on the number of (CTAT) repeats. The cutoff was the presence of atleast 10 repeats corresponding to ≥(CTAT) and ≥(CTAT). The presence of more than or equal to 10 CTAT repeats was termed as the long allele in the group while for repeats less than 10 CTAT repeats were taken as the short allele. The group was again evaluated using the bimodal distribution and the three genotypes which were obtained were <10(CTAT) and ≥(CTAT). The presence of more than or equal to 10 CTAT repeats was termed as the long allele in the group while for repeats less than 10 CTAT repeats were taken as the short allele.
seen that the Lipid profile parameters seems to be increased in the presence of longer allele. Infact the cohort with the presence of longer allele had higher levels of TG (cutoff >= 150mg/dl) TC (cutoff <=200mg/dl) and LDL (cutoff>=150mg/dl). Although the TG, TC and LDL levels were all higher in individuals bearing the long allele however no statistical tests could be applied due to the small number of subjects in the group bearing the short allele. Thus it is noteworthy that the cases possessing the longer allele were have a higher prevalence of symptoms of multiple metabolic syndrome (MMS) like Hypercholesteremia, higher Systolic and Diastolic blood pressure with increased LDL levels, and decreased HDL levels.

APOE Gene Polymorphism in Rheumatoid Arthritis

Hasegawa et al found that the Apo E3/4 phenotype was significantly more common in the RA patients with amyloidosis (31.4%) than in the patients without amyloidosis (12.3%; P < 0.05) or in healthy controls (12.7%; P < 0.05). The frequency of the epsilon 4 allele was significantly greater in the group with amyloidosis (0.16) than in the patients without amyloidosis (0.07; P < 0.05) or in healthy controls (0.07; P < 0.05).

It was concluded that the presence of Apo E4 isoprotein may be a risk factor for the development of amyloidosis in patients with RA.

Maury et al concluded that the prevalence of the apoE4 isotype is not increased in patients with RA complicated by amyloidosis when compared with Finnish control subjects. Since the frequency of the apo epsilon4 allele is significantly decreased in RA patients without amyloid when compared with Finnish control subjects, the presence of the apoE4 in a patient with RA could, though, represent a relative risk factor for developing reactive amyloidosis.

To study the role of genetic variants of APOE gene among patients of rheumatoid arthritis we have examined alleles of the APOE gene. This gene exists in three different isoforms namely E*2, E*3, E*4. The APOE gene is located on the long (q) arm of chromosome 19 at position 13.2. More precisely, the APOE gene is located from base pair 50,100,878 to 50,104,489 on chromosome 19.

Our cohort was analyzed using a case control design on 179 cases and 149 controls. The distribution of the allelic and genotypic frequency is described in Table 5 and Figure 5-6. The alleles showing significant difference in the cases and controls are marked. The population was in HWE in controls (p>0.05). Maximum frequency allele was E*3 in those with DAS score < 6 and >6, while minimum frequency allele was E*2-2 followed by E*2-3 in both groups. No significant association was seen with the APOE polymorphism and disease severity Table 6.

Conclusion

This exploratory study has looked at the role of APOE gene and D2S430 STR marker, D2S439, in susceptibility for Rheumatoid arthritis a metabolic disorder with a high heritability index. Several studies have looked at specific candidate genes and chromosomal markers contributing to the risk for RA in European and American populations, however no such attempt has been made by rheumatologist or molecular biologist in India. In that aspect this is the first study of its kind. The salient results that this pilot study highlights are:

1. The north Indian population, specifically from western Rajasthan differs from the Caucasian population in the most prevalent allele of the, D2S439 marker.
2. The long allele of this marker representing an expansion of the CTAT, tetranucleotide repeat doubles an individual’s risk for developing RA.

3. The same allele also contributes to an elevated total cholesterol, triglyceride and LDL levels in this cohort of RA patients.

4. The same allele also contributes to elevated systolic blood pressure in patients of RA.

5. APOE gene on the other hand does not seem to impact the risk for developing RA and the severity of the disease.

To the best of our knowledge it is the first study in this part of the world. The study definitely needs to be extended to larger cohort of patients and control samples and to a larger set of candidate genes and/or STR markers. Extending the studies to a larger cohort will also allow genetic analyses of clinically defined endophenotypes observed in the patients of this chronic metabolic disease with attributes of autoimmune disorder and multiple symptoms in patients. Genetic studies can also impact strategies adopted for effective personalized treatment for this progressively debilitating disease.

References

In Type 2 Diabetes Uncontrolled on Dual therapy

START EARLY — STEP UP — SYNERGIZE

Glycomet Trio 1
Methaformin 850 mg OR + Glypiptide 1 mg + Vaglbose 0.2 mg

Glycomet Trio 2
Methaformin 1000 mg OR + Glypiptide 2 mg + Vaglbose 0.2 mg

STEP UP

Glycomet Trio 2/0.3
Methaformin 1000 mg OR + Glypiptide 2 mg + Vaglbose 0.3 mg

In Obese Type 2 Diabetes Uncontrolled on Dual therapy

Glycomet Trio Forte 2
Methaformin 1500 mg OR + Glypiptide 3 mg + Vaglbose 0.2 mg

Also available

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Ecosprin® AV 150/20
(Enteric Coated Aspirin 150 mg + Atorvastatin 20 mg)
Hematological, Biochemical and Renal Changes in Patients of Multiple Myeloma Treated with Bortezomib Based Triple Drug Chemotherapy

Tribikram Panda1*, Sidhartha Das2, Rabindra Kumar Jena3, Bidyut Prava Das4, Sashi Bhusan Rout5

Abstract

Introduction: Multiple myeloma (MM) is a neoplasic clonal plasma cell disorder. Approximately 30% of newly diagnosed MM present with baseline renal dysfunction adversely affecting prognosis and survival. But its outcome has improved with the advent of novel agents.

Methods: We undertook this clinicopathological study to assess the profile of renal involvement, evaluate hematological response, renal reversibility and renal response of 34 newly diagnosed cases of MM with renal impairment receiving 4-6 cycles of Bortezomib, Thalidomide and Dexamethasone (BTD).

Results: Bone pain (67.64%) and pallor (88.23%) were the most common clinical symptom and sign respectively. Mean serum creatinine before and after treatment was 3.5 mg/dl and 1.59 mg/dl respectively. After treatment 15 cases achieved renal reversal, 8 patients had improved renal function and 3 patients became dialysis independent. The median time to renal reversal was 22weeks (2-28 weeks) and overall myeloma response rate was 78.78%. All patients showed renal response. The median time to renal response was 2.4weeks. We found 38.23% pure cast nephropathy, 14.7% myeloma immunoglobulin deposition disease (MIDD), 5.88% amyloidosis apart from other lesions.

Conclusions: BTD is safe, effective in reversing renal impairment and improves survival in newly diagnosed cases of MM with renal impairment.

Introduction

Multiple myeloma (MM) is a neoplasic clonal plasma cell disorder comprising a spectrum of diseases ranging from monoclonal gammopathy of unknown significance (MGUS) to plasma cell leukemia. It is associated with monoclonal protein in the blood or urine with concomitant organ dysfunction [1].MM accounts for approximately 1.3% of all malignancies in whites and 2% in blacks. Again 13% and 33% of all hematological malignancies in whites and blacks respectively are attributed to MM [2].

Approximately 30% of newly diagnosed MM present with baseline renal dysfunction [3]. Nearly (1-13) % of patients present with frank renal failure with subsequent dialysis dependency and 50% of patients with MM have reduced creatinine clearance at presentation [4]. Tubular casts, monoclonal light chains, hypercalcemia, amyloid deposition, dehydration, hyperuricemia, analgesic abuse and other nephrotoxic drugs, infections, tumour lysis syndrome during treatment all account for the renal impairment.

Renal affection in myeloma not only affects prognosis but also shortens the survival leading to early mortality. Recent introduction of safe and effective novel agents have improved the survival even in patients with renal impairment.5,6 Bortezomib, a novel proteasome inhibitor, is very much active in relapsed and refractory MM. But its use and impact on reversibility of newly diagnosed patients with MM and renal failure has not been studied much.

A team work with multimodality approach is often needed for successful outcome particularly in a resource poor setting. In view of insufficient data on Indian myeloma patients, we undertook this clinicopathological study to observe hematological, biochemical and renal changes in patients of newly diagnosed multiple myeloma with renal impairment treated with BTD. The purpose of this study is to assess the effect and reversibility rate of renal function in newly diagnosed patients of MM with renal impairment who were treated in our institution with BTD.

Material and Methods

Inclusion criteria

Newly diagnosed cases of MM (diagnosed according to the International Myeloma Working Group Revised Diagnostic Criteria) with renal impairment were included in the study [7]. Renal impairment was defined as serum creatinine ≥2 mg/dl at diagnosis and/or estimated glomerular filtration rate (eGFR) <50ml/min/1.73 m² calculated by MDRD (modification of diet in renal disease) equation.8

Exclusion criteria

Patients with history of Diabetes, pre existing hypertension, MGUS (monoclonal gammapathy of undetermined significance), SMM (Smoldering Multiple Myeloma), Solitary plasmacytomas, nonsecretory myelomas, light chain myelomas were excluded from the study.

All our patients were evaluated with detailed history, general and systemic
examinations, hematological and biochemical parameters, bone marrow study, serum protein electrophoresis and immunofixation, estimation of serum free light chains (FLC) ratio, urine analysis and 24 hr urinary protein estimation. Ultrasonography guided renal biopsy was done in all cases (n=34) with prior informed written consent before starting treatment for documenting the type of renal lesion in MM. Post treatment renal biopsy was also performed in few cases (n=6) to see the subtle changes in renal histopathology with bortezomib therapy apart from its clinical outcome.

**Treatment protocol**

All our patients received 4-6 cycles of bortezomib (1.3 mg/m² S.C, weekly), thalidomide (200 mg/day, oral) and dexamethasone (40 mg once a week, oral) depending on response. Each cycle was of 4 wk duration. All patients were assessed for sustained reversibility of renal failure (renal effect persisting for at least 2 or more months) on above mentioned 4-6 cycles BTD regimen with other supportive measures. Hemodialysis was offered to all patients with an appropriate indication.

**Criteria for reversal of renal function**

Reversal of renal function was defined as sustained (maintained for at least 2 month) decrease in s.creatinine to <1.5 mg/dl after above treatment. Improved renal function was defined as when s.creatinine didn’t normalise, but decreased by ≥50% from baseline as when s.creatinine didn’t normalise, but decreased by ≥50% from baseline as when s.creatinine didn’t normalise, but decreased by ≥50% from baseline as when s.creatinine didn’t normalise, but decreased by ≥50% from baseline. Improved renal function was defined as sustained (maintained for at least 2 month) decrease in s.creatinine to <1.5 mg/dl after above treatment.

**Renal response**

All patients were eligible for assessment of improvement of renal function based on changes in eGFR as shown in Table 1.1

Renal function was assessed in every clinic visit or more frequently if indicated. After treatment all patients were evaluated for the type of haematological (myeloma) response in accordance with the revised uniform response criteria by the International myeloma working group apart from above renal response.10

**Statistics**

All statistical analysis and calculations were done using SPSS version 20. A p value of <0.05 was considered statistically significant.

**Results**

The baseline characteristics of the patients are shown in Table 2. The mean age was 51.94 years with 19(55.88%) males and 15(44.11%) females. All our patients had Durie salmon stage III disease and 94.12% had ISS stage III disease.

The clinical profiles at the time of presentation are depicted in Table 3. All patients in our study had renal impairment (as per inclusion criteria) and 18(52.94%) patients in our study presented with subjective complaint of renal dysfunction in the form of decreased urination. Renal impairment was not the presenting feature and detected incidentally during evaluation in rest of the patients.

Changes in hematological and biochemical parameters before and after treatment are depicted in Table 4. As shown, 90.9% of the study population had Hb value <10g/dl. The baseline Hb (7.9±1.41 g/dl) and post treatment Hb (10.2± 0.92 g/dl) showed statistical significance (p <0.001). Thirty (90.9%) of our patients had serum creatinine values ≥2 mg/dl. The mean s.creatinine before (3.5±1.71 mg/dl) and after treatment (1.59±0.58 mg/dl) were significant statistically (p<0.001). Renal reversibility (s.creatinine <1.5 mg/dl) was achieved in 15(45.45%) cases. The median time to reversal of renal function was 22weeks (2-28 weeks). Eight (24.24%) patients had improved renal function. Rest 10(30.30%) patients showed reduction in s. creatinine but less than 50% from the baseline. Out of 8 cases receiving hemodialysis, 3(37.5%) became dialysis independent at the end of 4-6 cycles of BTD. One patient died during 5th cycle and one lost to follow up.

The mean baseline eGFR was 20.54 ml/min/1.73 m² with 72.72% of cases were having estimated GFR between (15-30) ml/min/1.73 m². Post treatment eGFR was 48.87 ml/min/1.73 m² (p<0.001).Mean baseline creatinine clearance (by Cockroft-gault formula) and post treatment values were 25.5 ml/min and 44.91 ml/min respectively (p <0.001). In 3 of our patients serum cystatin C was measured. The mean baseline serum cystatin C was 2.005 mg/dl and post treatment value was 1.04 mg/dl.

Out of 33 cases, 29.41% showed complete renal response, 12.12% showed partial renal response, 57.57% cases showed minor renal response. The median time to onset of renal

---

**Table 1: Renal responses according to improvement of GFR**

<table>
<thead>
<tr>
<th>Renal response</th>
<th>Change in GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRenal (Complete renal)</td>
<td>From &lt; 50 mL/min to ≥60 mL/min</td>
</tr>
<tr>
<td>PRenal (Partial renal)</td>
<td>From &lt; 15 mL/min to 30-59 mL/min</td>
</tr>
<tr>
<td>MRenal (Minor renal)</td>
<td>From &lt; 15 mL/min to 15-29 mL/min</td>
</tr>
<tr>
<td>From 15-29 mL/min to 30-59 mL/min</td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 2: Baseline demographics and pretreatment characteristics of the patients (n=34)**

<table>
<thead>
<tr>
<th>Age in years (Mean±SD)</th>
<th>51.94±8.83</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>19(55.88%)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>15(44.11%)</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>22.04</td>
</tr>
<tr>
<td>Mean Body Mass Index</td>
<td>30.05 (kg/m²)</td>
</tr>
<tr>
<td>Median disease duration (months)</td>
<td>4.2(0.1-10)</td>
</tr>
<tr>
<td>Median ECOG performance status (0-5)</td>
<td>3 (range 2-4)</td>
</tr>
<tr>
<td>Median Karnofsky performance status</td>
<td>50 (range 50-70)</td>
</tr>
<tr>
<td>Myeloma subtype (IgG-kappa /IgG-lambda /IgA kappa)</td>
<td>26(76.4%) / 7(20.58%) /1(2.94%)</td>
</tr>
<tr>
<td>Median baseline marrow plasma cells (%)</td>
<td>53% (13-94)</td>
</tr>
<tr>
<td>Mean baseline serum M protein (g/dl)</td>
<td>4.90 ± 1.97</td>
</tr>
<tr>
<td>Durie salmon staging</td>
<td>All stage III</td>
</tr>
<tr>
<td>ISS staging (Stage II/III)</td>
<td>2 (5.88%) / 32 (94.12%)</td>
</tr>
<tr>
<td>ECOG-Eastern Cooperative Oncology Group performance status, ISS- International Staging System</td>
<td></td>
</tr>
</tbody>
</table>

---

**Table 3: Clinical profile during presentation (n=34)**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>23(67.64%)</td>
</tr>
<tr>
<td>Fatigue, malaise</td>
<td>18(52.94%)</td>
</tr>
<tr>
<td>Renal dysfunction (oliguria, anuria)</td>
<td>18(52.94%)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>11(32.35%)</td>
</tr>
<tr>
<td>Fever( recurrent infections)</td>
<td>5(14.70%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3(8.82%)</td>
</tr>
<tr>
<td>Anaarca</td>
<td>3(8.82%)</td>
</tr>
<tr>
<td>Localized mass</td>
<td>2(5.88%)</td>
</tr>
<tr>
<td>Pathological fractures</td>
<td>2(5.88%)</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>2(5.88%)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>1(2.94%)</td>
</tr>
<tr>
<td>Cord compression</td>
<td>1(2.94%)</td>
</tr>
</tbody>
</table>

---

**Table 4: Clinical profile during presentation (n=34)**

<table>
<thead>
<tr>
<th>Signs</th>
<th>n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pallor</td>
<td>30(88.23%)</td>
</tr>
<tr>
<td>Lytic bone lesions</td>
<td>13(38.23%)</td>
</tr>
<tr>
<td>Pedal edema</td>
<td>11(32.35%)</td>
</tr>
<tr>
<td>Bleeding manifestations</td>
<td>2(5.88%)</td>
</tr>
<tr>
<td>Severe dehydration</td>
<td>2(5.88%)</td>
</tr>
</tbody>
</table>
Table 4: Hematological and biochemical changes before and after BTD (n=33)

<table>
<thead>
<tr>
<th>Parameters n (%)</th>
<th>Baseline (Mean±SD)</th>
<th>After BTD (Mean±SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10 - 30 (90.9%)*</td>
<td>7.9±1.41</td>
<td>10±0.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥10 - 3 (9.1%)*</td>
<td>9588±4731.56</td>
<td>8578±2124.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>TLC* (/mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100×10³ (2.4%)</td>
<td>152000±112702</td>
<td>168666.7±9916.2</td>
<td>0.227</td>
</tr>
<tr>
<td>≥100×10³ - 21 (63.64%)*</td>
<td>74.18±41.79</td>
<td>63.15±26.71</td>
<td>0.091</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2-3 (30.9%)*</td>
<td>3.5±1.71</td>
<td>1.59±0.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥2-30 (90.9%)*</td>
<td>10.59±1.76</td>
<td>9.79±0.96</td>
<td>0.021</td>
</tr>
<tr>
<td>S.Creatinine (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2-3 (9.1%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2-30 (90.9%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S.B. (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;11-22 (66.7%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥11-11 (33.3%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15-7 (21.2%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-30-24 (72.72%)*</td>
<td>20.58±8.30</td>
<td>48.87±18.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>31-60-26 (0.06%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)**</td>
<td>25.50±15.81</td>
<td>44.91±16.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.07±0.59</td>
<td>3.25±0.46</td>
<td>0.012</td>
</tr>
<tr>
<td>S(B) microglobulin (mg/L)</td>
<td>8.66±3.05</td>
<td>27.4±0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SLDH (u/l)</td>
<td>1018.03±435.54</td>
<td>319.81±122.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP(Q) (mg/dl)</td>
<td>38.51±17.27</td>
<td>19.97±9.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S Uric acid (mg/dl)</td>
<td>6.17±2.6</td>
<td>5.35±2.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S.Cystatin C (mg/l)</td>
<td>n=3</td>
<td>2.05±0.84</td>
<td>0.025</td>
</tr>
<tr>
<td>S.24 hr urinary protein (gms/day)</td>
<td>0.99±1.8</td>
<td>0.50±0.77</td>
<td>0.016</td>
</tr>
</tbody>
</table>

* values indicate baseline values at time of presentation, estimated Glomerular Filtration Rate by Modification of Diet by Renal Disease equation, ** Calculated by Cockroft-gault formula

Table 5: Change in involved light chains and free light chain (FLC) ratio with treatment

<table>
<thead>
<tr>
<th>Involved light chain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline* (mg/L)</td>
</tr>
<tr>
<td>Kappa n=26</td>
</tr>
<tr>
<td>Lambda n=7</td>
</tr>
<tr>
<td>S.Calcium(mg/dl)</td>
</tr>
</tbody>
</table>

Table 6: Renal histopathology and response (n=34)

<table>
<thead>
<tr>
<th>Renal pathology</th>
<th>n (%)</th>
<th>Renal response</th>
<th>Myeloma response</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCN</td>
<td>13(38.23%)</td>
<td>4 CR renal/2 PR renal/7 MR renal</td>
<td>sCR/CR,4 VGPR, 4 PR</td>
</tr>
<tr>
<td>MIDD</td>
<td>5(14.70%)</td>
<td>2 CR renal/3 MR renal/3 CR</td>
<td>2 VGPR</td>
</tr>
<tr>
<td>MCN/MIDD</td>
<td>3(8.82%)</td>
<td>1 CR renal/1 MR renal</td>
<td>1 MR (3 CR)</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>2(5.88%)</td>
<td>MR renal (1 VGPR)</td>
<td>1 PR</td>
</tr>
<tr>
<td>MCN/Amyloidosis</td>
<td>2(5.88%)</td>
<td>MR renal (1 VGPR)</td>
<td>1 death</td>
</tr>
<tr>
<td>MCN/Chronic interstitial nephritis</td>
<td>2(5.88%)</td>
<td>1 PR renal</td>
<td>1 MR (1 VGPR)</td>
</tr>
<tr>
<td>Cryoglobulinemic nephropathy</td>
<td>1(2.94%)</td>
<td>CRrenal (sCR)</td>
<td></td>
</tr>
<tr>
<td>MCN/Cryoglobulinemic nephropathy</td>
<td>1(2.94%)</td>
<td>CR renal (CR)</td>
<td></td>
</tr>
<tr>
<td>MCN/MPGN</td>
<td>1(2.94%)</td>
<td>MR renal</td>
<td></td>
</tr>
<tr>
<td>Acute Tubular Necrosis (ATN)</td>
<td>2(5.88%)</td>
<td>CR renal (all 2 sCR)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2(5.88%)</td>
<td>1 CR renal/1 MR renal</td>
<td></td>
</tr>
</tbody>
</table>

response was 2.4 weeks (1.14-10.28 weeks). Accessing myeloma response, 9.09% cases showed sCR (stringent complete response), 42.42% showed CR (complete response), 27.27% showed VGPR (very good partial response), 18.18% showed PR (partial response), 3.03% showed PD (progressive disease).

Three patients who achieved sCR myeloma response achieved CRenal response. Out of 14 CR myeloma responses, 7 showed CRrenal, 3 showed PRrenal, 4 achieved MRrenal response. Out of 9 patients who achieved VGPR, 8 showed MRrenal and 1 showed PRrenal response. All other patients showing PR, PD myeloma responses achieved MRrenal response. The overall response rate (sCR, CR, VGPR) in our study was 78.78% after 4-6 cycles of BTD. The cumulative probability of survival at end of 80wks (18m) was 92%.

Out of 4(11.76%) cases showing nephrotic range proteinuria, one patient died during treatment and 1(3.03%) patient continued proteinuria in that range even after treatment. Rest two patients showed definite reduction in proteinuria. Mean proteinuria both baseline and post treatment was 0.99 Gms/day and 0.50 Gms/day respectively for the study cohort. The change in free light chain (FLC) and FLC ratio with treatment is depicted in Table 5.

** MM affects the kidneys by both paraprotein mediated and nonparaprotein mediated injury. The spectrum of histopathological renal involvement, corresponding renal and myeloma response to treatment is shown in Table 6.**

### Discussion

MM is a disease of elderly with median age being 72 years (range 43-88 years). The younger age (51 years) of presentation of our patients was in accordance with several studies which clearly suggest the role of some unknown environmental/genetic factor involved with myeloma genesis in our patients living in India. The high incidence of anemia in MM can be due to anaemia of chronic disease, erythropoietin deficiency, due to renal impairment, bone marrow suppression by cytokines and chemotherapeutic agents, bleeding diathesis and direct malignant infiltration of bone marrow. In our study, 88.23% had hemoglobin less than 10Gm/dl. Though bortezomib has no direct effect on hemoglobin, the improvement after treatment in our study could be due to the supportive therapies (iron, folic acid, transfusions when indicated) and overall improvement of patient’s general condition after treatment.

Three (9.09%) cases presented with baseline leucopenia (TLC<4000/µL and 3(9.09%) of them had count <50000/µL. Direct marrow involvement, corresponding renal and myeloma response is depicted in Table 5. In our study, 88.23% had hemoglobin less than 10Gm/dl. Though bortezomib has no direct effect on hemoglobin, the improvement after treatment in our study could be due to the supportive therapies (iron, folic acid, transfusions when indicated) and overall improvement of patient’s general condition after treatment.

Bone pain (67.64%) and pallor (88.23%) was the most common clinical symptom and sign respectively (Table 3) in accordance with several other studies. The high incidence of pallor in our patients may be due to associated renal dysfunction present in all our patients and comitant iron deficiency highly prevalent in our community apart from other causes of anemia in MM. The cause of anaemia in MM can be due to anaemia of chronic disease, erythropoietin deficiency, due to renal impairment, bone marrow suppression by cytokines and chemotherapeutic agents, bleeding diathesis and direct malignant infiltration of bone marrow. In our study, 88.23% had hemoglobin less than 10Gm/dl. Though bortezomib has no direct effect on hemoglobin, the improvement after treatment in our study could be due to the supportive therapies (iron, folic acid, transfusions when indicated) and overall improvement of patient’s general condition after treatment.
causes of thrombocytopenia in MM. Despite thrombocytopenia in above mentioned subjects we didn’t delayed treatment with bortezomib. Unlike standard cytotoxic therapy bortezomib causes transient thrombocytopenia with short recovery time without any lethal cytotoxic effect on megakaryocytes [16]. Mean platelet count recovered rapidly between treatment in a cyclical fashion and in bortezomib responders, baseline platelet count increased significantly during subsequent cycles.

Serum cystatin C has been regarded as a sensitive marker of renal impairment in MM. The reduction in serum cystatin C with bortezomib clearly signifies effectiveness of bortezomib in improving renal function.

The antiproteinuric effect of Bortezomib is due to inhibition NF kβ pathway, decreased TGF β levels and down regulation of collagen, TIMP-1 (tissue inhibitor of metalloproteinase 1) production. Thus it inhibits progression of renal glomerulosclerosis, improves glomerular function and reduces proteinuria. All our cases showed renal response. Even patients who had partial myeloma response and progressive disease too showed MRenal response with some improvement in serum creatinine. This may be due to above renoprotective effect of bortezomib apart from independent antimonyeloma activity.

MM affects the kidneys by both paraprotein mediated and nonparaprotein mediated injury. The profile of renal histopathological involvement among our patients was in accordance with other studies. One patient with MPGN didn’t do well with our treatment and ultimately died 27 days after completing five cycles of BTD with supportive dialysis.

Repeat renal biopsy of those MCN cases achieving CR showed definite reduction in the median number of casts (24 vs. 13 per 10 fields before and after treatment respectively). But the extent of interstitial fibrosis and tubular atrophy were similar. Degree of renal impairment was not significantly predictive of probability of renal response, but higher baseline median casts per field, diffuse tubular atrophy and interstitial fibrosis, renal amyloidosis and MPGN all were having poor renal response and outcome.

With BTD, drug related nausea and vomiting was the most common adverse effect noted in 22(64.7%) cases followed by fatigue in 13(38.23%), peripheral neuropathy in 10(29.41%), somnolence in 8(23.52%), leg swelling in 6(17.64%), diarrhea in 3(8.82%), infection, hepatic dysfunction, constipation each in 2(5.88%) cases and dyspnoea, herpes zoster, arthralgia, deep vein thrombosis, skin rash each in 1(2.94%) of case. Anemia and thrombocytopenia were the most common hematological adverse effects, each noted in 2(5.88%) cases followed by neutropenia in 1(2.94%) case. Most of our patients were anemic during presentation and had low baseline hemoglobin even after treatment. So those patients who showed 2 Gm/dl reduction of hemoglobin from previous pretreatment values were only counted to have therapy (BTD) related anemia (5.88% cases). All the adverse effects were of grade 1/2 (mild to moderate) according to National cancer institute common toxicity grading and managed conservatively.

One patient had grade 3(severe) thrombocytopenia with melena during 4th treatment cycle requiring delaying of subsequent cycle of bortezomib by 14 days after receiving supportive therapy and platelet transfusions. Treatment was restarted after normalization of platelet count. These observations suggested that BTD can be safely used in MM patients with renal impairment and poor performance status.

Conclusion

MM presents a decade earlier in Indian patients compared to their western counterparts.BTD is effective in reducing proteinuria, reversal of renal failure and significantly improves renal outcome thereby improving survival apart from achieving prompt treatment response in newly diagnosed MM with renal impairment. It’s safe with acceptable adverse effect profile. Future longitudinal studies involving larger number of patients with cytogenetic assays and histopathological correlation in high risk myeloma patients will help in better understanding of the treatment outcome in MM.

Acknowledgment

We would like to thank all the patients and the family members, the data collectors and the laboratory technicians who participated in the study.

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Use of Disease Activity Score (DAS28) and Routine Assessment of Patient Index Data 3 (RAPID3) for Assessment of Rheumatoid Arthritis Disease Activity, in the Indian Setting

Aditi Shah¹, Seema Kini²*, Vikram Londhey³

Abstract

Introduction: Patient outcomes in rheumatoid arthritis (RA) have significantly improved with the advent of disease modifying anti rheumatic drugs and the newer biological agents. Various scoring systems available for monitoring disease activity in RA have not yet been put into full use in patient management in India. We aim to study the disease activity score 28 (DAS28) and Routine assessment of patient index 3 (RAPID3), their correlation and patient outcomes in RA.

Materials and Methods: The study was conducted between March 2011-May 2011. A total of 81 patients were included. Patient’s history was noted. Clinical examination for tender and swollen joint counts was performed. DAS28 was calculated. MDHAQ was administered to each patient in a language they understood and responses noted. Correlation between DAS28 and RAPID3 was studied using Pearson’s correlation coefficient.

Results: RAPID3 and DAS28 showed Pearson’s correlation coefficient of 0.8699 (p<0.001). Of the 53 patients who met with DAS28 severity criteria of >5.1, 82.7% showed similar results with RAPID3 suggesting severe disease activity. (X² = 33.512 and p<0.001). A greater proportion of those whose DMARD initiation was 2 years after disease onset, had higher disease activity as compared to those with earlier initiation.

Conclusion: Early diagnosis and immediate initiation of aggressive DMARD therapy should be the protocol. Regular patient outcome assessment using either of the two proposed scoring systems can be a good adjunct to physician’s clinical judgment in treatment decisions.

Introduction

Rheumatoid arthritis is a chronic inflammatory disease predominantly affecting synovial joints. With the advent of disease modifying anti rheumatic drugs and newer biological agents, patient outcomes have improved. In a disease that could be only symptomatically treated earlier with the use of NSAIDS and steroids, we can now think of targeting a remission. The diagnostic criteria and treatment strategy for RA has seen a major change over the last few decades. The hit early hit hard approach is the most favoured.¹,³

Rheumatologists worldwide prefer using early DMARD therapy including methotrexate singly or in combination with other DMARDS, once RA is diagnosed.⁴,⁵ This prolonged treatment with DMARDs including addition of biologics needs regular patient follow up and assessment of disease activity. There are various scoring systems for monitoring patient outcomes in RA. These scoring systems which were previously used mainly in clinical trials, are now finding their place in clinical practice, worldwide. These have not yet been put into full use in patient management in India. They give an accurate measure of the disease activity of the patient that can be documented during each follow up visit, thus guiding treatment decisions along with the physician’s judgment, which on its own may lack reproducibility.

Two such scoring systems include the disease activity score 28 (DAS28) and Routine assessment of patient index data 3 (RAPID3). While DAS28 is an objective clinical measure which is obtained using a formal joint count, RAPID3 is a patient answered questionnaire, a part of multi dimensional health assessment questionnaire (MDHAQ).

DAS28 is calculated after conducting a formal joint count by a physician during each follow up visit of the patient and disease activity is documented. RAPID3 score includes only the three patient-reported American College of Rheumatology (ACR) core dataset measures for RA: physical function, pain, and patient global estimate of status. It does not involve a formal joint count. It is thus answered by the patient before visiting the rheumatologist in most of the western countries providing the physician with a disease activity score at the beginning of each visit.

The use of the above mentioned scoring systems can thus aid in making better treatment decisions. However, the relevance of the same in an Indian setting is not fully established, due to presence of only few Indian studies.

We therefore aimed at studying the correlation between DAS28 and RAPID3 scores, patient outcome in terms of disease activity using these scoring systems, and in turn study the suitability and applicability of these scoring systems in the Indian setting.
Results

Off the 81 patients included in the study, 70 were females and 11 were males, with a male to female ratio of 1:6.36. Thirty eight of 81 patients showed the presence of various deformities.

The correlation between DAS28 and RAPID3

RAPID3 and DAS28 have a Pearson’s correlation coefficient of 0.8699 and p<0.0001 suggesting considerable correlation (Figure 1).

Also, cross-tabulation studies were performed on the two scoring systems. Patients falling into DAS28 severity criteria as defined as a score of more than 5.1, and RAPID3 severity criteria as defined as a score of more than 12 were compared. It is observed that of the 53 patients who met with DAS28 severity criteria of >5.1, 82.7% showed similar results with RAPID3 i.e., they had a score of more than 12 suggesting severe disease activity. Also 86.2% of patients who had DAS28 score of less than 5.1 suggesting moderate to less disease activity or remission had a RAPID3 score of less than 12 suggesting the same.

The chi square value for these was 33.512 and p<0.0001, considered highly significant (Table 1).

Additional analysis was performed to note the effect of delay in starting DMARD therapy on disease activity using DAS28 and RAPID3. Patients were divided into 2 groups. Group 1 with a delay of less than or equal to 2 years and Group 2 with a delay of more than 2 years.

Thirty eight of 45 patients (84.4%) in whom treatment was delayed by more than 2 years after disease onset (group 2) recorded a severe disease activity of >5.1 on DAS28 while 61.1% of patients from group 1 had their DAS28 score less than 5.1 (Table 2). Recorded difference being statistically significant. Comparing this with the results obtained with RAPID3, it is observed that similarly significant results are obtained. Thirty five of 45 patients from group 2 recorded severe disease activity of >12 on RAPID3 and 58.3% patients from group 1 had RAPID3 scores of <=12, the observed difference being statistically significant (Table 3).
Discussion

The present study shows that DAS28 and RAPID3 significantly correlated. This suggests that DAS28 a quantitative measure of disease activity obtained by a formal tender and swollen joint count, and RAPID3 (MDHAQ) give similar results of disease activity of patients. As the values obtained from RAPID3 match with those obtained from DAS28, which is considered as a highly specific measure of RA disease activity, RAPID3 can be conveniently used in as an important aid in routine clinical decisions.

Similar results have been obtained in multiple foreign6-9 as well as few Indian studies that reveal significant correlation between DAS28 and RAPID3. In a study conducted by Singh et al (2012)10 they concluded that RAPID3 and DAS28 provide similar quantitative information and hence, can be used to monitor patients of RA and guide treatment decisions. However, their study included 200 literate patients which made it easier to calculate the score before the patient met the physician, taking around 10s. Present study being conducted in a tertiary care centre in Mumbai, the major bulk of patient population included were illiterate which made it necessary that each question be explained to them in a language they understood taking up around 3-5 minutes per patient. Hence, as in the present study, in similar set ups in India, MDHAQ will have to be separately administered to the patient by the doctor or the nursing staff and RAPID3 then calculated from it. This is where paramedical and nursing staff may also be included to help provide the much needed patient data during each follow up visits and in turn improve patient care. The advantage of having documented objective data far outweighs this minor hurdle and ensure more informed decisions on patient management.

When treatment strategies are concerned, it has been observed that DMARDs are particularly beneficial when the treatment is initiated as early as possible from the onset of disease symptoms, as has also been established by Furst DE et al,12 An intensive approach using the DMARDs as soon as the patient is diagnosed with rheumatoid arthritis can improve patient quality of life and significantly reduce morbidities.

In our study it has been observed that the effect of delay in starting DMARD therapy on disease activity shows similar results using DAS28 and RAPID3. Off the 45 patients initiating DMARD therapy after 2 years of onset of disease activity, 84.4% showed severe disease activity using DAS28 and 75.6% showed severe disease activity using RAPID3 again proving that RAPID3 gives similar results as DAS28 regarding patient disease activity.

With the Indian scenario as slightly different from the international one, it is the need of the hour, to ensure a more stringent approach towards patient care in rheumatoid arthritis. Inclusion of these scoring systems in daily clinical practice will definitely help to quantify disease activity. The DAS28 and RAPID3 seem to be of utility in our setting, with a minor disadvantage of being time consuming. However, both giving similar results, it can be the treating physician’s call as to which one suits best in their respective setting.

It can thus be concluded that early diagnosis and immediate initiation of aggressive DMARD therapy should be the protocol. Patient should be followed up using either of the two proposed scoring systems, and a regular record of the patient’s disease activity should be maintained. Treatment decision including dose titration/stepping up to biologics should be made using these records. Thus these scoring systems may be a good adjunct to a physician’s clinical judgment in the management of rheumatoid arthritis.

Acknowledgement

Indian Council of Medical Research.
Diagnostic Value of Low Platelets in Malaria

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Abstract

Objective: To study the incidence of thrombocytopenia in adults with Plasmodium vivax infection.

Method: An observational study comprising 84 consenting individuals with Plasmodium vivax infection was undertaken. All the individuals belong to armed forces who are from different parts of the country. Everyone had normal platelet count prior to admission to the hospital. After admission, they were subjected to routine hematological and biochemical investigations comprising complete blood count including platelet counts, urine routine, liver function test, renal function test, serum electrolytes and Chest X-ray after ruling out Dengue, concomitant sepsis and possibility of recent viral infection. Grading of thrombocytopenia was done according to NCI common terminology criteria for adverse events Version 3.0. Results were analysed and tabulated.

Result: A total of 84 patients were studied. 82 (97.6%) patients had thrombocytopenia. Majority (68.3%) of the patients had their lowest platelet count on the 5th and 6th day of fever. There was no associated increase in risk of complication with the increase in grade of thrombocytopenia. But with increase in severity of thrombocytopenia, it took more time for the platelets to recover to normal level.

Conclusion: Thrombocytopenia is widely present in P. vivax malaria of adults. However, the severity of thrombocytopenia does not correlate with the likely progression to complication. The chance of progressing to complicated malaria is equal among all adults of P.vivax malaria irrespective of the platelet levels. Hence, in a resource limited rural Indian set-up where the expertise to diagnose and detect malaria microscopically or reliable antigen detection method is not available, thrombocytopenia in an acute febrile illness especially on Day 5 to Day 6 of fever onset could be considered as P. vivax malarial infection with good amount of diagnostic accuracy (sensitivity of 97.6%) and empirical anti-malarial therapy could be started as per the existing treatment guidelines.

Introduction

Malaria, the disease known to have altered the course of humanity in the past has killed millions and many more have suffered from it. In the last 100 years of civilization, nearly 150 million to 300 million people have died of malaria, accounting for nearly 2% to 5% of all deaths.1 Ever since Sir Ronald Ross made his landmark discovery in 1897 at Secunderabad, India, the disease still remains un conquered. Even with definitive treatment available, malaria continues to kill thousands across the globe.

It is no more a fact that complicated malaria is caused by Plasmodium falciparum (P. falciparum) alone as Plasmodium vivax (P. vivax) can also lead to severe complicated malaria [2]. P. vivax infection is indicated in multiple organ failures as seen with P. falciparum.

The clinical profile of malaria varies widely and certain aspects are yet to be studied extensively. Thrombocytopenia in malaria is a known complication. However, there are not many studies done regarding thrombocytopenia in P. vivax especially in adults of Indian population. The percentage of people having low platelets in P. vivax according to various studies done across the globe varies from 40% to 78%.3,4 Many Indian studies are however carried out in paediatric population.

In this study, we analysed the extent of thrombocytopenia in P. vivax in Indian adult population. Also, we carried out the study to find any co-relation between the severity of thrombocytopenia and complicated malaria.

Material and Methods

Place of study
The study was conducted in the Department of Medicine, 15 Air Force Hospital from 01 Jun 2017 to 31 Dec 2017.

Study design
An observational study was undertaken.

Sample size
A total of 84 patients with P. vivax malaria were evaluated.

Inclusion criteria
1. The study comprised of all consenting individuals above the age of 18 years diagnosed to have P. vivax malaria by peripheral blood smear.
2. All individuals with prior normal platelet count.

Exclusion criteria
1. Patients less than 18 years of age.
2. Patients having either mixed infection with P. vivax and P. falciparum or mono-infection with P. falciparum alone.
3. Patients with concomitant sepsis, Dengue or any other undiagnosed
fever in the last 01 month.

4. All non-consenting individuals and individuals who withdrew consent during any part of the course of the study.

Study Design

A total of 108 patients were enrolled in the study. 12 patients were detected to have mixed malaria and hence excluded from the study. 03 patients had concomitant sepsis while presenting to the hospital and were also excluded from the study. Of the 95 individuals who were selected for the study after analysing the inclusion and exclusion criteria mentioned above, 11 individuals were not willing to participate after explaining the course of the study in the language they best understand.

All the individuals belong to armed forces who are from different parts of the country. Since it is mandatory to undergo initial medical examination in armed forces prior to recruitment which includes a complete blood count and also every individual undergoes annual medical examination which also includes complete blood count, it is clear that everyone had normal platelet count prior to admission to the hospital.

All eligible patients who have consented to the study were subjected to routine hematological and biochemical investigations comprising complete blood count including platelet counts, urine routine, liver function test, renal function test, serum electrolytes and Chest X-ray. All patients were also checked for Dengue infection using NS1 antigen based card test. Patients requiring specialized investigation like ultrasound abdomen, CT scan of brain and arterial blood gas analysis (ABG) were done as per requirement.

Diagnosis of malaria was done through detection of malaria parasite (P. vivax) in peripheral blood smear. Complete blood count including platelet counts were done using 5 part Sysmax Hematology analyser.

Grading of thrombocytopenia was done according to NCI common terminology criteria for adverse events Version 3.0. Results were analysed and tabulated.

Result

A total of 108 patients were enrolled in the study. After analyzing the inclusion and exclusion criteria, 84 eligible patients consented for the study.

The mean age of the study population was 34.2 ± 9.10 years with 78.6% of them being under 40 years of age.

Of the 84 patients, 82 patients (97.62%) had thrombocytopenia (platelets less than 1.5 lakhs per mm³ as per NCI common terminology criteria for adverse events Version 3.0). Frequency distribution of grades of thrombocytopenia in the study population is depicted in Figure 1/ Table 1. Lowest platelet count observed among the study population showed negatively skewed distribution, with the median platelet count being 58,500 cells/mm³ of blood.

About 39% of the patients were admitted on the 4th day of fever while 21% were admitted on 3rd day, 20% on 5th day, 11% on 6th day, 5% on 7th day, 2% on 8th day and 1% on 10th day of fever. Majority (68.3%) of the patients had their lowest platelet count on the 5th and 6th day of fever with 37.8% and another 30.5% of the patients were found to have lowest platelet count on 5th and 6th day of fever respectively. 12.2% of the patients had their lowest platelets on the 4th and 7th day each while only 6.1% of them had on the 8th day. A meager 2.4% were found to have the lowest platelet count on the 3rd day and only 1.2% on the 10th day of fever. The distribution of lowest platelets in respect to the day of fever onset is shown in Figure 2.

<table>
<thead>
<tr>
<th>Thrombocytopenia grade</th>
<th>Platelet count/mm³ of blood</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>≥150,000</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Grade I</td>
<td>75,000 - 150,000</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Grade II</td>
<td>50,000 - 75,000</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Grade III</td>
<td>25,000 - 50,000</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Grade IV</td>
<td>≤ 25,000</td>
<td>4</td>
<td>4.8</td>
</tr>
</tbody>
</table>
The study showed that a majority (68.3%) of the patients had their lowest

Table 2: Frequency distribution of total leucocyte count (TLC)

<table>
<thead>
<tr>
<th>TLC/mm³</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1500-4000</td>
<td>36</td>
<td>42.9</td>
</tr>
<tr>
<td>4001-6500</td>
<td>45</td>
<td>53.6</td>
</tr>
<tr>
<td>6501-9000</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>9000-11500</td>
<td>1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

involving platelet specific antibodies \(^{12}\) and damage due to oxidative stress. \(^{13}\) Though the possibility exists that thrombocytopenia may be due to decreased thrombopoiesis, the presence of normal megakaryocytes in the bone marrow literally rules out this possibility. Our study showed an incidence of thrombocytopenia in 97.6% cases (82 out of 84 cases). Few studies done recently in adults also showed that thrombocytopenia is more common in P. vivax malaria. \(^{15,16}\) The results are contrary to the conventional notion that P. falciparum malaria causes severe thrombocytopenia than P. vivax malaria.

In our study, though thrombocytopenia was noted in 97.6% cases, there is no associated increase in risk of complication with the grade of thrombocytopenia. None of the 82 patients who had thrombocytopenia developed any bleeding complication. While 02 cases of complicated malaria had low platelets, 02 cases with normal platelets also progressed on to complicated malaria showing no relation to the extent of thrombocytopenia and risk of complication. The most commonly observed complication was hypotension. This result is contrary to the findings exhibited by George P et al.\(^{17}\) Bhatia V et al,\(^{18}\) Harish R et al,\(^{19}\) Kakar A et al\(^{20}\) and Arti Muley et al\(^{21}\) where low platelets were associated with increased complication. However, majority of these studies have reported the complications occurring in children and our study comprises of adult Indian population in their second and third decade of life with mean age 34.2 ± 9.10 years.

In our study, majority of the patients were admitted on Day 3 and Day 4 of onset of fever. After confirmation of diagnosis by peripheral blood smear, Chloroquine was started to all on the same day of admission to the hospital. Similar studies conducted did not mention about the day of onset of fever in context to treatment.

The study showed that a majority (68.3%) of the patients had their lowest

Discussion

Malaria is a true hematologic disease and affects all blood cell lines. Anemia and thrombocytopenia are the most common hematologic complications associated with malaria. Thrombocytopenia in malaria is a known complication. However, there are not many studies done regarding thrombocytopenia in P. vivax especially in adults of Indian population. The percentage of people having low platelets in P. vivax according to various studies done across the globe varies from 40% to 78%. \(^{3,4}\) Also, the conducted studies implicate that the likelihood of the febrile illness being malaria is 12 to 15 times higher if the platelet count is less than 1.5 lakhs/mm\(^3\).\(^{3,4,7}\)

Our study analysed the association between thrombocytopenia and P. vivax infection in which low platelets (platelets less than 1.5 lakhs/mm\(^3\)) was seen in 97.6% cases Figure/Table 1. Other studies done by Colonel et al,\(^{8}\) Jamal et al\(^{9}\) and NK Gupta et al\(^{10}\) reported thrombocytopenia in a significantly lesser proportion of 72%, 72% and 78% respectively. However, NK Gupta et al and Colonel et al conducted their study in paediatric population. There are also few worldwide studies conducted in children who reported much lower incidence of thrombocytopenia in malaria like 40%\(^{7}\) and 59%.\(^{10}\)

The precise mechanism by which thrombocytopenia occurs in malaria is unknown. The fact that P. vivax is no less serious than P. falciparum is well established after the advent of molecular diagnosis.\(^{2}\) The possible explanations for the occurrence of low platelets in malaria are due to direct lytic effect of the parasite on the platelets,\(^{11}\) immune mediated mechanisms

In 76.9% of patients with Grade I Thrombocytopenia, platelets returned to normal level between Day 8 to Day 11 while in Grade II thrombocytopenia, 80.7% patients recovered between Day 10 to Day 12 while a similar trend is seen in Grade III thrombocytopenia where 76.9% patients recovered between Day 10 to Day 12. In Grade IV Thrombocytopenia, normal platelets were seen between Day 11 to Day 13. The graph depicting time period for platelet recovery in various grades of Thrombocytopenia is depicted in Figure 3.

Total leukocyte count (TLC) dropped to less than normal in 42.9% of the patients. The drop is seen between 4\(^{th}\) to 8\(^{th}\) day of fever in 82% of the patients. The TLC was also found minimum on 3\(^{rd}\) day of fever in 9.5%, 4\(^{th}\) day in 18%, 5\(^{th}\) day in 26%, 6\(^{th}\) and 7\(^{th}\) day in 13% each, 8\(^{th}\) day in 12%, 9\(^{th}\) day in 5% and 10\(^{th}\) day in 4% of the patients. The frequency distribution of total leukocyte count is depicted in Table 2.

Mean haemoglobin on the day of lowest platelet count was observed to be 13.17±1.30 g/dl which was within the normal limits for adult males.

A significant proportion of patients had hyperbilirubinemia with normal serum aminotransferases. 38.1% (32/84 patients) had hyperbilirubinemia. The percentage of people with hyperbilirubinemia increased with the severity of thrombocytopenia. While none in grade 0 had hyperbilirubinemia, only 12.0% (03/25) had in grade I. On the contrast, 44.4% (12/27) in grade II, 57.7% (15/26) in grade III and 50.0% (02/04) in grade IV had hyperbilirubinemia with normal serum aminotransferases (Table 3).
platelet count on the 5th and 6th day of fever. The distribution of lowest platelets in respect to the day of fever onset is shown in Figure/Table 2. This is in contrast to the findings of Arif M et al where thrombocytopenia was common among the initial days (Day 1 to Day 4).\textsuperscript{22} Also, comparing various similar studies, there were no conclusions drawn about the relation of onset of fever to the day of lowest platelets which is a novelty of our study.\textsuperscript{21,22}

We observed in our study that the time period for platelets to return to normal levels (>1,50,000/\text{mm}$^3$) varied with the degree of thrombocytopenia. With increase in severity of thrombocytopenia, it took more time for the platelets to recover to normal level. While in about 80% of patients with Grade I Thrombocytopenia platelets returned to normal level between Day 8 to Day 11, a similar proportion in Grade II and III thrombocytopenia recovered between Day 10 to Day 12 whereas in Grade IV Thrombocytopenia, it was between Day 11 to Day 13. The results are no surprise since it takes longer time for lowest levels of platelets to return to normal.

In our study, Chloroquine was started very early in the disease course (majority on Day 3 and Day 4 of onset of fever). Whether the time period for platelet recovery is related to early starting of Chloroquine treatment requires further elaborate studies since none of our patients presented after Day 10 of onset of fever.

There is a significant association between low platelets and high bilirubin levels with normal transaminases observed in our study. While 02 cases with normal platelets had no liver function abnormality, 38% of cases with low platelets had elevated bilirubin with normal transaminases. This is consistent with the results of Arti Muley et where 35.7% had hyperbilirubinemia.\textsuperscript{21}

Further, the percentage of people with hyperbilirubinemia increased with the severity of thrombocytopenia. The rise in bilirubin was transient with none progressing to acute liver cell failure and normal serum bilirubin was observed after four to six days of afebrile period. However, whether an increase in bilirubin alone with normal transaminases is associated with risk of complication cannot be commented upon by our study.

Conclusion

Thrombocytopenia is widely present in $P$. vivax malaria of adults. However, the severity of thrombocytopenia does not correlate with the likely progression to complication. Our study shows no co-relation between the grade of thrombocytopenia and complication. The chances of progressing to complicated malaria is equal among all adults of $P$.vivax malaria irrespective of the platelet levels. Rightly so, thrombocytopenia is not a criteria to define complicated malaria. Also, platelet value tends to reach the lowest on Day 5 to Day 6 of onset of fever.

Even in the modern era of medicine, we are heavily dependent on slide method to detect malaria since none of the antigen based malaria detection kits are reliable. Slide detection method requires hands of well trained and experienced lab technicians. The HRP-2 and pLDH based rapid detection kits failed to detect malaria in blood samples with parasite load more than 5000 per microlitre. Hence, in a resource limited rural Indian set-up where the expertise to diagnose malaria microscopically or reliable antigen detection method is not available, thrombocytopenia in an acute febrile illness especially on Day 5 to Day 6 of fever onset could be considered as $P$. vivax malarial infection with good amount of diagnostic accuracy (sensitivity of 97.6\%) and empirical anti-malarial therapy could be started as per the existing treatment guidelines. Though the presence of thrombocytopenia is not a specific finding to malaria, the endemicity of malaria in the region with the presence of thrombocytopenia could be a guiding factor for treatment.

But the presence of thrombocytopenia in $P$. vivax malaria in different Indian geographical locations needs to be studied extensively before formulating a treatment guideline for starting to treat malaria based on thrombocytopenia.

References


\begin{table}
\centering
\caption{Percentage breakdown of people with elevated bilirubin in various grades of thrombocytopenia}
\begin{tabular}{|l|c|c|}
\hline
Thrombocytopenia grades & Normal bilirubin & Hyperbilirubinemia \\
\hline
0 (n=2) & 2 (100) & 0 \\
1 (n=26) & 21 (80.8) & 5 (19.2) \\
II (n=26) & 15 (57.7) & 11 (42.3) \\
II (n=26) & 10 (38.5) & 16 (61.5) \\
IV(n=4) & 1 (25) & 3 (75) \\
\hline
\end{tabular}
\end{table}
The Novel Biomarkers in Diabetes

Amita Diwaker1, Dhiraj Kishore2, Vivek Singh3, Satya Prasad Mahapatra3

Abstract
According to International Diabetes Federation, the worldwide prevalence of impaired glucose tolerance (IGT) in adults is 318 million and is expected to reach 482 million by 2040. With increasing burden of prediabetes and their expectant progression in diabetes has compounded the problem. Now question is that how we can identify the subjects at high risk to develop prediabetic state and among them who will rapidly progress into diabetes? Once a person diagnosed to be a diabetic then there are only few marker which can depict development of diabetes related complications and also to help in preventing such diabetes related complication progression. In this article, we will review several biomarkers used to predict the risk of progression to prediabetes, diabetes states in context to their mechanism of action, sensitivity, specificity, advantages, disadvantages and association with dysglycemia. The risk stratification arising due to insulin resistance by novel biomarker will improve clinical outcome both in prediabetics and diabetics.

Introduction
In coming days diabetes Mellitus will be a major health problem for the world, with its highest impact on newly industrialized, developing nations and minority groups in developed countries.1 Diabetes will increase from 135 to 300 million worldwide between 1995 and 2025, of which (93-97%) will be type II diabetic patients mounting a 42% increase in diabetes and overall 27% increase in the prevalence globally.2 Not only diabetics but the pre diabetics will be compounding the problem. According to Centers for Disease Control one out of three, adults had prediabetes which is an intermediate state and agonizingly, 90% were unaware of their diagnosis.3 In 2015, the International Diabetes Federation estimated that the worldwide prevalence of impaired glucose tolerance (IGT) in adults was 318 million and expected to reach 482 million by 2040.4 The subject in question is how can we identify patients with prediabetes early and can we prevent progression to diabetes? Identification of these prediabetes states and risk stratification arising due to insulin resistance by novel biomarker will improve clinical outcome both in diabetics and pre diabetics.5 The Finnish Diabetes Prevention Study6-7 and the U.S. Diabetes Prevention Program8-9 have shown that changes in dietary habits, weight loss, and increased physical activity reduced the risk of progression to diabetes. So, the tools to identify and making an individual aware of his prediabetes state is need of time. Biomarkers for risk stratification, diagnose prediabetes and prevent complication in diabetes. Factors leading to prediabetic state are genetics, peripheral IR, defects in insulin secretion, glucotoxicity, lipotoxicity, impaired incretin release, amylin accumulation, inflammation, oxidative stress, and decreased β-cell mass leading to β-cell dysfunction.10-12 Prediabetes includes isolated impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).13 However the differing criteria of WHO and ADA made issue controversial as slight changes in criteria leads of large long term outcome.14,15 Hence review of biomarker will give better understanding of disease course and therapeutic interventions.

Current diagnostic biomarkers and their clinical utility.

Hemoglobin A1c: It’s advantage and disadvantages
A better chronic glycemia estimation is done by HbA1c rather than glucose levels at a single time point. The ADA diabetes criteria cut off are HbA1c ≥6.5% (48 mmol/mol) and 5.7–6.4% (39–46 mmol/mol) for prediabetes.13 High HbA1c levels were also associated with increased CVD and all-cause mortality in Norfolk prospective study.16 Advantages of HbA1c over FPG and oral glucose tolerance test (OGTT) includes greater convenience as fasting is not needed, pre-analytical stability not required, and have minimal day-to-day fluctuation during periods of stress and illness.17 However, there is conflicting evidence regarding the usefulness of HbA1c as it provides moderate sensitivity in diabetes diagnosis when compared to OGTT and FPG.17,18 Moreover OGTT more strongly correlates with IR and insulin secretion than HbA1c.19 The NHANES and Screening for Impaired Glucose Tolerance studies showed HbA1c levels <5.7% (39 mmol/mol) correlates only 60–70% of subjects having normal glucose tolerance (NGT).20,21 Additionally HbA1c threshold for prediabetes does not take ethnicity, body mass index (BMI), and age, all of which may significantly alter HbA1c levels under consideration.22 Changes in the production rate or circulating life span of red blood cells will affect HbA1c levels.23 Falsely low HbA1c occurs in hemolytic anemia, blood loss,25,26 splenomegaly, and end-stage renal disease.27 Hemoglobin variants, such as Hbs, Hbc, Hbd, and Hbe may also result in overestimation or under-estimation of HbA1c.28 So HbA1c alone can be inadequate for diagnosing prediabetics, and more accurate
diagnosis may require confirmation with other biomarkers.\textsuperscript{31}

Fructosamine: Is it a better glycemic marker?

Fructosamine (FA) is used as an alternate glycemic marker for diabetes screening and it is also useful to diagnose prediabetes. It reflects mean blood glucose level of previous 1–4 weeks.\textsuperscript{28} FA is also useful in conditions which affects hemoglobin levels. This method is cost effective and convenient to perform.\textsuperscript{32,33} It have high variability method is cost effective and convenient to perform.\textsuperscript{32,33} It have high variability.

It is also a good indicator of the risk for microvascular complications.[35] But few studies deny it to be useful, for prediabetes screening.\textsuperscript{29,31-36-38} In conclusion, conditions where HbA1c is inaccurate FA can be used as a valuable complementary marker.

Glycated albumin: Why and when to prefer over FA?

Although it is similar to FA, glycated albumin (GA) is definitely better indicator of glycemic control than HbA1c in individuals having renal failure, hemolytic anemia, and blood transfusions cases.\textsuperscript{31,33} As GA quantify the ratio of GA to total albumin,\textsuperscript{39} so GA is a preferable choice to FA in clinical conditions like nephrotic syndrome, chronic liver disease, and thyroid disorders.\textsuperscript{39} However the combination of GA with HbA1c have better sensitivity to predicts prediabetes than HbA1c alone.\textsuperscript{38} Drawback is that, sometimes GA may be artificially low in individuals having increased BMI, body fat mass, and high visceral fat.\textsuperscript{40} Still the mechanism for variation in GA quantification in these conditions is poorly understood.\textsuperscript{41}

1,5 Anhydroglucitol (1,5 AG): Is it better postprandial hyperglycemia and complication predictor?

1,5 Anhydroglucitol, is a monosaccharide, identified as a prediabetes marker. Renal Proximal tubules have relatively greater affinity for glucose than 1, 5 AG, so hyperglycemia prevents 1, 5 AG reabsorption leading to increased 1, 5 AG urinary concentration. So, plasma 1, 5 AG concentrations lowers as plasma glucose increases as reflected in healthy control, prediabetes and diabetes groups.\textsuperscript{42} Alike FA, 1, 5 AG is a better biomarker as it reflects glucose levels within 2 weeks.\textsuperscript{43} Other advantages are it is stable, reproducible, and cost effectiveness than other glycemic diagnostic tests.\textsuperscript{43} It is better used in identifying postprandial glycemic excursions and those having risk of complications in context to retinopathy and microvascular and macrovascular episodes in diabetes. However, its level fluctuates in individuals on renal replacement therapy or receiving SGLT 2 inhibitor.\textsuperscript{44,45} On contrary few studies do not recommends use of 1, 5 AG as a prediabetes screening tool.\textsuperscript{46-44}

Now the Novel Biomarkers

Adiponectin: A helper from fat tissue

Adiponectin, is formed from adipose tissue, it has insulin-sensitizing, anti-inflammatory, and anti-atherogenic functions and it is shown to be independent predictor of diabetes.\textsuperscript{47} Concentration of adiponectin are inversely related to IR (insulin resistance) and obesity.\textsuperscript{47} Lower level of adiponectin was observed even a decade prior to development of diabetes or its complications specially in men.\textsuperscript{47} In offspring of diabetic parents, the baseline adiponectin levels are inversely related to the risk of prediabetes and it is independent of sex or ethnicity.\textsuperscript{48} Hyperinsulinemic Euglycemic clamp and intravenous glucose tolerance test, showed that adiponectin levels were directly correlated with higher insulin sensitivity and indirectly with insulin concentration.\textsuperscript{48}

Fetuin-A

Fetuin-A (FetA) is a glycoprotein secreted from liver ,it correlates with increased risk of T2DM incidence and it’s complications.\textsuperscript{49} Importantly, unlike adiponectin, the EPIC-Potsdam prospective cohort study established, FetA as a independent risk marker after normalization of the BMI and waist circumference for T2DM.\textsuperscript{49} FetA promotes lipid-induced IR through the toll-like receptor 4 (TLR4)-inflammatory signaling pathway leading to production of inflammatory cytokines.\textsuperscript{50} Pal et al showed that FetA binds to TLR4, and regulates insulin sensitivity through this interaction.\textsuperscript{50} High-fat diet-fed FetA knock down animal module have less TLR4-mediated signaling in adipose tissue causing IR, with FetA injection in this model induces inflammatory signaling and IR. Presence of FetA and TLR4 both needed for FFA (free fatty acid) induced inflammatory cytokine expression in adipocytes. Higher FetA is also correlating with risk of cardiovascular disease in candidates susceptible IR.\textsuperscript{51} In conclusion FetA acts as an endogenous ligand for TLR4 for induction of IR by lipids. Hence FetA may therefore serve as a novel therapeutic target for IR.

Metabolites and amino acid: The hidden cytalyzer

Amino acids. Branched chain amino acids (BCAAs).: The good one and the bad one for diabetes Isoleucine, leucine, valine, tyrosine, aromatic amino acid phenylalanine and glycine have been significantly associated with development of diabetes.\textsuperscript{52,53-56} Glutamine, methionine, cysteine, and 2-aminoacidic acid are increased in initial insulin-resistant states.\textsuperscript{57-59} Contrarily glycine levels are lower in prediabetic individuals.\textsuperscript{60-62} These changes in circulating amino acid levels may prove to be significant predictive biomarker for IR and T2DM.

α-Hydroxybutyrate (α-HB).

α-Hydroxybutyrate (α-HB) is a catabolic by product of threonine , methionine and glutathione anabolism (cysteine formation) in hepatic tissue.\textsuperscript{63} Increased oxidative stress and lipid oxidation leads to chronic shifts in glutathione synthesis resulting in elevated α-HB levels in individuals of IR.\textsuperscript{64-65} It is reflected by increased urinary α-HB excretion in IR.\textsuperscript{66} α-HB can be used as a biomarker to distinguish NGT-insulin-sensitive (NGT-IS) individuals from IGT and IFG individuals and NGT-IS individuals from those with NGT-IR individuals.\textsuperscript{67} Hence it can be an effective and promising biomarker for prediabetes.\textsuperscript{68}

Lipoprotein(a)

Lipoprotein(a) is synthesized by liver. Elevated levels of LP(a) is proved to be independent risk factor for development of CVD.\textsuperscript{67} Serum Lp(a) and the prevalence of prediabetes and T2DM have inverse relationship.\textsuperscript{68} Although the mechanism is not clear higher insulin may play a role in reducing Lp(a) concentration.\textsuperscript{68}

Triglycerides and high-density lipoprotein.

In prediabetics significant increment in levels of small HDL3 particles compared to HDL-C levels have been observed.\textsuperscript{69} Small HDL3 particles is
positively relates with triglyceride and negatively relates with HDL-C. HDL-C induces insulin secretion and low HDL-C promotes progression of prediabetes to diabetes however, it is not clear whether HDL-C levels plays a role in β-cell dysfunction or not.

Ceramide

Ceramide a lipid molecules mediate IR. It acts through inhibiting insulin action by decreasing phosphorylation. Further it accumulates in insulin-resistant tissues and induce inflammation through activation of TNF-α. Studies also showed, ceramide propagates coronary artery disease.

Ferritin and transferring

Storage and iron release are regulated through an intracellular protein ferritin. There is an association of high serum ferritin and transferrin saturation with increased risk of prediabetes and diabetes. Mechanism being the catalytic iron induces formation of reactive oxidative molecules causing hepatic dysfunction, and β-cell apoptosis, which contribute to IR. Dietary iron restriction prevents the development of diabetes and loss of β-cell function. However the threshold levels of ferritin which correlate with IR is not certain.

Mannose binding lectin serine peptidase and thrombospondin 1

High levels of MAS1 found in prediabetes, diabetes, and the CVD. Even onset of prediabetes and IR occurred earlier in those with higher MAS1 plasma levels. Elevated FPG and 2-hour glucose levels have positive association with higher levels of MAS1. Other markers like thrombospondin 1 (THBS1) and glycosylphosphatidylinositol-specific phospholipase D1 (GPLD1) are also increased in prediabetes. Thrombospondin have inflammatory properties, and contributes to higher prediabetes prevalence.

Acyl-carnitine

Serum levels of acyl-carnitines have been shown to be elevated in prediabetes. Although the role of acyl-carnitine in FAO and its mechanism in IR are not clear. It has been postulated that abnormal of FAO and mitochondrial function leads to accumulation of intermediary products such as acyl-carnitines which promotes inflammation and IR.

MicroRNAs: The hidden player

MicroRNAs (miRNAs) are small, noncoding RNAs participating in post-transcriptional gene expression. These are involved in many biological processes such as growth, development, differentiation, proliferation, and cell death. Recently, miRNAs have been studied in pre-diabetes and found to be strongly correlated. In particular miR-192 and miR-193b high levels observed in prediabetics. miR-193b plays critical roles in differentiation of brown adipocytes and inflammation reduction in IR. Elevated levels of both miRNAs i.e., miR-192 and miR-193b were observed with IFG and IGT and it also correlated with Tg levels and the fatty liver index in animal models. It is quite significant as a fatty liver can be associated with prediabetes. Other miRNAs significantly elevated in T2DM are miR-9, miR-29a, miR-30d, miR-124a, miR-146a, and miR-375, all of these play a role in β-cell dysfunction. These miRNAs negatively regulate insulin expression and secretion. Few miRNAs levels are low in prediabetes, of these microRNA-126, miRNA-15a is found in endothelial cells and it is quite low in IGT/IFG and T2DM. miR-15a is thought to regulate and promote insulin formation by inhibiting endogenous uncoupling protein-2 gene expression and increasing insulin secretion. So, miR-15a have a significant role in β-cell function and insulin synthesis.

Inflammatory markers: The universal culprits

IL-6 and CRP higher concentration is associated with a greater risk of diabetes development. These inflammatory markers are useful in identifying individuals at higher risk of developing T2DM. Tissue plasminogen activator-1 (PAI-1) changes is an independent predictor of incidence of diabetes. IL-18 level increased parallel to progression from prediabetes to diabetes in the Gutenberg study. Levels of IL-1RA were found to be significantly elevated even 13 years prior to the diagnosis of diabetes and it raises more rapidly about 6 years prior to diagnosis even after adjusting for obesity. The Whitehall Study, showed an increase in IL-1RA in prediabetes in parallel with decreasing insulin sensitivity, increasing β-cell function, and 2-hour glucose levels, all of which occurred altogether years before the development of T2DM.

White blood cell count, fibrinogen, and hematological indices: Subtle indicator

A high WBC count predicts worsening insulin action, insulin secretion, and diabetes development in Pima Indians. The neutrophil-lymphocyte ratio (NLR) has also been associated with both microvascular and macrovascular complications in diabetes.

Conclusions and Prospective

Dysglycemia is a continuous pathophysiologic process. It is overtly underestimated and puts large number of individuals at risk for full blown disease state. With development of hyperglycemia it is already late in the evolution to T2DM leading to uninhabitable micro-macrovacular complications. β-cell function markedly reduced leading to progressively rising glucose levels, on higher side of “normal glycemic range”. So there is a vital need to identify and use sensitive precise biomarkers to predict progression to dysglycemia at the earliest, when β-cell function is optimally functional. Interference at this stage may be more responsive to lifestyle modification and pharmacological agents. A well identified set of biomarkers in a clinical practice will give better sensitivity and specificity in prediabetes and diabetes complication prediction. Comparative studies of biomarkers will help to ascertain their clinical utility. Furthermore, genetic studies assessing mutations will also provide additional insight into associations with metabolic deregulation.

Abbreviations

HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; BMI, body mass index; FA, fructosamine; GA, glycated albumin; OGTT, oral glucose tolerance test; IR, insulin resistance; 1, 5 AG, 1, 5 anhydroglucitol; FetA, fetuin-A; TLR4, toll-like receptor 4; T2DM, type 2 diabetes mellitus; α-HB, alpha-hydroxybutyrate; α-KB, α-ketobutyrate; L-GPC, L-alpha glycerylphosphorylcholine; Lp(a), lipoprotein(a); HDL-C, high-density lipoprotein cholesterol; HDL-LpPLA2, HDL-associated lipoprotein-associated phospholipase A2; MBL, mannos binding lectin; CVD, cardiovascular disease; THBS1, thrombospondin 1;
GLP1, glycosylphosphatidylinositol-specific phospholipase D1; NF-kB, nuclear factor-kB; miRNA, microRNA; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; CRP, C-reactive protein; IL, interleukin; WBC, white blood cell; NLR, neutrophil-lymphocyte ratio; PAI-1, plasminogen activator inhibitor-1; IL-1RA, IL-1 receptor antagonist; SGLT2, sodium-glucose co-transporter 2.

References

Enhancing Medication Adherence through Improved Patient-provider Communication: The 6A’s of Intervention

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Abstract
Public-health facilities in the developing world often experience a high patient burden, low doctor-patient ratio, drug stock-outs and the lack of avenues for adequate patient-provider communication. We identified strategies for enhancing medication adherence for chronic disorders in Indian health settings that rely on improving patient-provider communication through a review of the literature. These include (A)sk the patient on adherence status, (A)ssess accurately medication adherence, provide (A)ssistance with regimen and enlisting support from all available resources especially family support, (A)nticipating and precluding interruption in adherence, (A)ssurance against harm due to drug side-effects and finally (A)void blaming the patient for non-adherence.

Introduction
Poor medication adherence is recognized as a major public health challenge especially in non-communicable chronic disorders that require a lifetime of regular medication intake. According to a World Health Organization estimate, nearly half of patients with chronic diseases are non-adherent to their medications. The Lancet medical journal states that “50% of the diagnosed Type-2 diabetes patients are prescribed suitable medications, and 50% of those are adherent”. Community-based studies from states in South India which have a comparatively better functioning health care system have also reported high rates of medication non-adherence in diabetes and hypertension patients. It is well-established that suboptimal medication adherence precludes the complete benefit of treatment but also increases the risk of hospitalizations and other adverse health outcomes in patients resulting in enormous economic losses. It is thus estimated that enhancing medication adherence interventions could substantially improve the population health and lower healthcare costs, perhaps more than any other treatment intervention.

Various strategies to augment medication adherence have been previously explored but usually in...
the context of the developed world. Their advanced healthcare systems have usually achieved universal health coverage, have adequate staffing and dedicated dietary and health counselors, patient waiting and queuing periods are low, electronic health and pharmacy records maintain updated records for patient health status, attendance and drug refills and digital aids to support adherence like text-message services are available to patients. In contrast, patients in a developing country like India often experience overcrowded public-health facilities with high patient burden, low doctor-patient ratio, drug stock-outs and the lack of avenues for adequate patient-provider communication. Moreover, the public health program for prevention and control of non-communicable diseases usually lack emphasis on promoting medication adherence. It is therefore essential to identify measures which are likely to work in resource-constrained public health settings. In this review, we discuss specific strategies to enhance medication adherence which could be utilized by providers operating in these settings for improving patient medication adherence.

**Methods**

We conducted a narrative review of the literature. The headings “medication adherence” or “medication compliance” AND “Diabetes”/”Hypertension” along with the keyword “India” was used to search MEDLINE (2009-17) and SCOPUS (2009-2017). The barriers and challenges in maintaining good medication adherence and causes for poor adherence were identified from these studies. Subsequently, we evaluated globally recognized patient communication strategies to enhance medication adherence which would also be applicable in the Indian context.

**Results**

The strategies identified for enhancing medication adherence in Indian health settings were grouped into the followed six categories relating to patient-provider communication and all beginning with the letter ‘A’.

1. **Ask**: The treating provider should preferably probe for non-adherence on each clinic visit by querying the patient on his or her medication intake behavior. Avoid a leading question like, “you are taking all your prescribed medications, aren’t you?” since it encourages patient self-desirability bias. Medication non-adherence should be suspected in the presence of adverse health outcomes relating to the disease like poor glycemic control or uncontrolled blood pressure, if the medication is known to cause significant side effects and also if the medication-casts are high and patients finds them difficult to afford.

2. **Assess**: providers must accurately assess the extent of medication adherence in their patients. Medication adherence has been defined “the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen”. The word extent signifies that non-adherent behaviour instead of being a ‘dichotomous all or nothing phenomenon’ ranges from taking too few or excess medication doses, symptomatic variation (drug avoidance on feeling better or worse) or even drug holidays due to pill refill failures. The primary estimation of medication adherence can be made through patient self-report by asking, “Patients often have difficulties in remembering to take all their medications? Have you missed any pills in the past week?”. The empathetic statement in the beginning normalizes patient behaviour and encourages them to tell the truth rather than provide inflated estimates to gratify his provider. Proceed by validating patient accuracy in reporting the dosing frequency. Furthermore, It is essential to estimate medication adherence for different disease conditions separately in the comorbid patient and not assume that adherence for one disease would correlate with another just because the medicines are supposed to be taken at the same time. Another simple way of assessing adherence is to ascertain the frequency of missed appointments in patient who collect refills post-appointment like in most public health facilities in India. Patients can then be probed on whether they were able to acquire their medication refill during the period when they had missed appointment. An effective method to assess medication adherence especially in patients with poor health literacy is to ask them to identify the medicine from its appearance (like the ‘small white pill’) although caution must be exercised to confirm the patient is referring to the correct medicine.

3. **Assist**: patients often require assistance in taking medications as prescribed by the provider, especially those who have multiple comorbidities, the elderly and patients with poor health-literacy. Since regimen complexity is known to undermine medication adherence, it is advisable to simplify the patient’s regimen by matching them with to their activities of daily living, preferably food-intake. Reducing the pill-burden can aid patients which is possible through fixed-dose combination but the formulations must have evidence supporting efficacy and safety. Enlisting family support when available is vital and can improve medication adherence by helping patients remember to take their medications, direct assistance in injecting the drug as in insulin and also through ways of motivation. In a study in an outpatient setting of a major tertiary care center in Delhi, it was found that patients who acknowledged family support in remembering their medications, reported higher medication adherence. In the technologically adept patient, use of mobile phone reminders can also be encouraged as a cues to action.

4. **Anticipate**: the provider in the resource-constrained setting should anticipate non-adherence by the patient and take steps towards its prevention. Economically vulnerable patients are particularly vulnerable to non-adherence when they fail to acquire drugs from public health facilities on being unable to keep appointments or lack of supplies. Studies from outpatient settings of public health facilities in India show a much higher
rate of medication adherence compared to studies conducted in rural settings which suggests non-adherence is more likely to be an unintentional phenomenon arising from lack of drug access.\textsuperscript{6,9,16,17} In circumstances when the provider perceives the patient may slide into non-adherence, there is need to emphasize the need to maintain continued adherence to prevent adverse health outcomes.

5. Assure: Patients may lose their belief in effectiveness of their treatment regimen at some point in time. Fear of drug side effects, whether real or perceived can also impair medication adherence. A study in an urban cross primary care clinic in New York City observed that diabetes patients whose disease and medication beliefs were inconsistent with a chronic disease model had suboptimal medication adherence.\textsuperscript{18} A study from the Gujarat state of India found 38.4% patients in a primary care facility lacked awareness that diabetes could not be cured and required lifetime medication.\textsuperscript{19} A study among Indian hypertensive patients found that those who perceived higher susceptibility to disease complications and perceived more benefit of treatment also reported higher rates of adherence.\textsuperscript{20} Effective patient-provider communication which dispels patient concern over their medication can go a long way towards improving their adherence to medications.

6. Avoid blame: blaming the patient for poor medication adherence is counterproductive and fails to take into account the shared collaboration between the patient and provider which is required to achieve optimum adherence. Furthermore, since, adherence can be unintentional and non-modifiable like due to aging, impaired memory, and absence of social support, it reflects a failing and lack of understanding on the part of the physician. Instead of according blame, providers should consider the factors contributing to non-adherence and whether those could have been ameliorated through effective communication which empowers the patient and promotes his understanding of the disease pathophysiology and complications resulting from the failure of adherence.\textsuperscript{21} For instance, some hospital-based studies from India have shown poor knowledge of diabetes and lack of awareness of complications in patients which indicate the neglected state of health communication prevalent.\textsuperscript{19-21} Some studies have found that paramedical staff is effective in imparting education and stimulating behavior change in patients in clinic-settings with the high patient load.\textsuperscript{22-23} The distribution of responsibilities of chronic disease patient counseling with nurses and pharmacists in the resource-constrained setting can thus be a valuable aid towards improving patient adherence. Furthermore, certain comorbid conditions like depression in diabetes or cardiovascular disease patient can independently lower medication adherence for which patients should be screened.\textsuperscript{24-25}

Conclusion

Poor medication adherence is a global problem but its determinants show considerable variation between the developed and the developing world primarily due to issues of drug access. The developed patient-provider communication can promote medication adherence in patients of chronic diseases by adopting specific strategies. These include early and regular assessment of medication adherence, assistance with regimen and enlisting support from all available resources especially family support, anticipating and precluding interruption in adherence, assurance against harm due to drug side-effects and finally avoiding blaming the patient for non-adherence.

References

Right Sided Heart: Seeing Beyond the Chest Radiograph

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35 year old female presented to the Department of Pulmonary Medicine, Government Medical College and Hospital, Chandigarh, with history of shortness of breath since childhood with seasonal variation of symptoms. Chest examination revealed bilateral rhonchi. Cardiac sounds, though normal, but were heard on right side. Spirometry showed reversible airflow limitation consistent with bronchial asthma. Chest radiograph showed cardiac shadow on the right side (Figure 1). Since the patient had bronchial asthma and right sided heart, keeping the possibility of Kartagener syndrome and/or allergic bronchopulmonary aspergillosis (ABPA) in mind, she was specifically investigated for any situs inversus/bronchiectasis. Contrast enhanced computed tomography (CECT) with high resolution cuts of chest showed thirteen pair of ribs bilaterally (Figure 2). There was collapse of right upper lobe, right pulmonary vein was seen draining into superior vena cava, the course of right pulmonary artery was tortuous with reduced calibre (10.8 mm) and there was dextropositioning of heart (Figures 3 and 4). Thus Partial anomalous pulmonary venous connection (PAPVC) was incidentally diagnosed. Suspecting an associated atrial septal defect with PAPVC, echocardiography was done which was found to be normal. Patient was reassured and treatment of asthma was optimised. As per the literature, such isolated PAPVC may be complicated with pulmonary hypertension and right heart failure in future hence close monitoring is required.² Patients need to be treated only when they develop these complications. Since PAPVC was asymptomatic in our patient, hence she was kept on close follow up.

A right sided cardiac impulse (during examination) with right sided heart on chest radiography should not be taken as confirmatory for dextrocardia. Since India is a high burden country for Tuberculosis, a right sided heart can just be a sequela subsequent to the disease/effective treatment.³ Collapse of the right lung, secondary to fibrosis or due to intraluminal occlusion (malignancy/foreign body) may give clinical impression of dextrocardia. Such causes can easily be clinched on detailed history, physical examination and other supportive radiographic features. However, further detailed work up of a right sided heart may still be required to differentiate various entities like dextropositioning, dextrocardia, dextrocardia with situs inversus and dextrocardia with situs inversus totalis.⁴⁵ Because of the association of a right sided heart with various cardiac and pulmonary anomalies,⁴ they should be thoroughly looked for, before reaching the final diagnosis. Adequate recognition of the pathology will facilitate in providing better and timely care, as was our patient where detailed work up of a right sided heart revealed it to be a mere dextropositioning rather than dextrocardia and an unknown

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Received: 02.02.2018; Accepted: 20.11.2018
extremely rare isolated PAPVC was clinched along with, guiding us to manage the patient in totality and follow her up in future.

References

Aorto-left Ventricular Tunnel

Rajeev Bhardwaj

Six years male child was admitted in pediatrics department of our institute. His parents noticed prominent precordial pulsations for few months. His BP was 120/60 mm Hg, pulse 76/min. Apex beat was in 5th intercostal space, in mid clavicular line. His heart sounds were normal. He had early diastolic murmur in left parasternal area, occupying about 50% of diastole. They made clinical diagnosis of aortic regurgitation. His echocardiographic examination was done. His aortic valve was found to be normal. There was evidence of aorto left ventricular (aorto LV) tunnel (Figure 1), with moderate regurgitation (Figure 2). Left ventricle was mildly enlarged and showed good contraction. Ejection fraction was 65%. The diagnosis was confirmed on cardiac catheterization. He was advised device closure of the defect but was lost to follow up.

The term “aortico-left ventricular tunnel” was used subsequent to Levy’s publication in 1963,1 and “aorto-left ventricular tunnel” was introduced about ten years later by Ross and colleagues.2 An aorto-ventricular tunnel is an extracardiac channel which connects the ascending aorta above the sinutubular junction to the cavity of the left or right ventricle. The usual presentation of the disease is during infancy or early childhood with heart failure symptoms due to chronic non-valvular aortic regurgitation and diastolic steal that starts right from the fetal life. Although a small number of patients are symptom-free and have survived to adulthood; most patients’ natural history of this lesion is progressive deterioration in heart function and death in the first year of life.3 Spontaneous closure in only one case with a slit-like tunnel is reported, but patients should be treated even if they have not any symptom. The tunnel is closed by surgery or with a device in appropriate patients. In these patients, ALVT can be closed using a proper device by cardiac catheterization.4

References
Abstract
We diagnosed a case of Takayasu arteritis (TA) involving subclavian arteries, the aorta, superior mesenteric artery and renal arteries presenting with stenotic, occlusive, and aneurysmal lesions along with mural thrombus, which responded well to ATD and steroids. We report this case as a rare combination of vascular lesions in a patient with a relatively rare variant of TA.

Introduction
TA is a chronic granulomatous panarteritis of large sized arteries, classically involving the aortic arch, but one third of the cases also affect the remainder of the aorta, its branches, and pulmonary arteries. We report a case of TA type V with extensive and varied involvement of the aorta and its branches that responded well to anti-tuberculosis drugs and steroids.

Case Report
A 28 year old unmarried non-diabetic, hypertensive lady, presented with the chief complaints of pain and numbness of both left limbs for four months and weakness of the same limbs along with low grade fever for the last one month. She was on Amlodipine 5 mg daily past 2 months and had been exposed to TB in her family 8 years back.

The patient was cachectic (BMI 17.3 kg/m²) and febrile on admission. The pulse rate was 82/min and radial and brachial pulsations were well palpable on the right side alone. Similarly, femoral, popliteal and dorsalis pedis arteries were palpable on the right side but not on the left. However, both carotid arteries were well palpable. The BP was 160/90 mmHg over the right brachial artery and 176/100 mmHg over the right popliteal artery. A longitudinal tubular mass with expansile pulsations involving the umbilical and hypogastric areas was appreciated with audible bruit over it. The power of left upper and lower limb was 4/5 in both proximal and distal group of muscles with normal tone without sensory involvement and preserved deep tendon reflexes.

The clinical examination was otherwise unremarkable. A provisional diagnosis of large vessel vasculitis with abdominal aortic aneurysm was entertained and investigations sent accordingly.

CBC revealed normal WBC counts, Hb 8.8 gm/dL, a microcytic hypochromic picture and an ESR of 120 mm at the end of one hour. Chest X-ray suggested superior mediastinal widening. Abdominal USG showed abdominal aortic aneurysm involving the entire length of the abdominal aorta, extending through the left common iliac artery into the left external iliac artery. The maximum diameter of the aneurysm was 6cm and effective luminal diameter was 2cm. Kidney sizes were normal. The diameter of induration on Mantoux test was 40mm. Sputum was unavailable and the Echo-Doppler study documented LVH and grade I diastolic dysfunction. ANA was negative by the Hep2 method.

CT angiography of aorta and its branches showed diffuse mural thickening with wall irregularity in the left subclavian artery and left axillary artery, chronic total occlusion of 2nd and 3rd parts of the left subclavian artery and tight stenosis of the left axillary artery (Figure 1). Marked tortuosity

Fig. 1: 3D CT angiography showing normal ascending and arch of aorta proximal to origin of left subclavian artery, long segment total occlusion of 2nd and 3rd parts of the left subclavian artery, tight stenosis of left axillary artery and focal moderate stenosis near origin of the coeliac trunk and total occlusion at origin of superior mesenteric artery

Fig. 2: CT angiography showing marked tortuosity and fusiform aneurysmal dilatations involving the entire descending thoracic and abdominal aorta, with acute angulations just above the aortic hiatus and at the infrarenal aorta

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Received: 16.11.2016; Accepted: 04.04.2019
Takayasu arteritis with extensive involvement of the aorta and its branches, with mural thrombus and aortic dissection, related to a Tuberculous etiology. Opinion from the Department of Cardio-thoracic and Vascular Surgery ruled out any operative intervention in such extensive vascular involvement. The patient was put on Category I anti-tubercular therapy along with oral prednisolone 40 mg daily for the initial 4 weeks, followed by tapering off over the next month. Fever subsided rapidly and the patient was put on physiotherapy and discharged after 3 weeks of hospitalisation. Six months later, there was substantial improvement of her left sided weakness with an appreciable increase in her claudication distance but no return of left sided pulses. The ESR at this time was 19 mm at the end of 1 hour.

Discussion

TA was first reported from Japan in 1908 and is prevalent in Asian populations. TA is a disease of young women (Male : Female 1 : 8, age of onset 25-30 years) and is the commonest cause of renovascular hypertension in India. The aortic arch is more involved in Japan while the involvement of the abdominal aorta is more in Indian and Korean patients. Common clinical and imaging features of TA are enlisted (Table 1).4

Our patient fulfilled the American College of Rheumatology criteria of TA (Table 2).4 The NIH has defined active disease as new onset or worsening of at least two of the following four features: (i) signs and symptoms of vascular inflammation or ischemia (claudication, decreased or absent pulses or blood pressure in the extremities, bruits or carotidynia); (ii) elevated ESR; (iii) angiographic abnormalities; and (iv) systemic symptoms like fever, polyarthralgia and polymyalgias not attributable to another disease. Vascular lesions in TA may be stenotic (93%), occluded (57%), dilated (16%), or aneurysmal (7%).5 This patient had stenosis, occlusion, and aneurysm, in addition to intra mural thrombus, a combination rarely seen in the literature. The Ishikawa clinical classification of Takayasu arteritis describes 4 groups depending on the number and severity of complications, and our patient could be categorized into Ishikawa Group 4.6 According to the new angiographic classification of TA as adopted at the Takayasu conference 1994, the aortic arch and its branches are mainly involved in Japanese patients (type I, IIa). But there was controversy regarding commonest type in India. According to few authors it is type IV7 and according to few it is type V.6 But a recent retrospective study clearly showed type V is the commonest type in India.6 Type III is the most common type found in south-east Asia and Africa and is called as ‘middle aortic syndrome’. Our patient had type V TA which is common in India.

The causal association of TA with TB has been much discussed. A 65 kDa heat shock protein (HSP) is a major immunogenic component of M. tuberculosis and expression of HSP has been shown to be strongly induced in the aortic tissue through molecular mimicry. It is possible that TA is caused by antibodies, generated following exposure of human host to bacterial HSP may cross-react with the human homologue of HSP 65, which is expressed on the surface of stressed endothelial cells. This interaction with the endothelial HSP may initiate an immune response responsible for the subsequent lesion.8,9

Higher frequency of positive tuberculin tests in TA patients than in general population were described in literature.10 Recently it was shown that skin delayed hypersensitivity to PPD with induration over 10 mm may be as frequent in TA as in patients with extrapulmonary tuberculosis (92.5% & 89% respectively).11

There is no correlation between the size of induration and likelihood of current active TB disease. But induration size of more than 15 mm are unlikely
Case of PUO, Psoas Abscess and Renal Failure

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Abstract
Pyrexia of unknown origin (PUO) is a common phenomenon. Abscesses are well known to present as PUO. We present a case of PUO due to psoas abscess and renal failure, with a rare manifestation of a common entity.

Introduction
Pyrexia of unknown origin is a common manifestation of abscesses, tuberculosis and malignancy. Abdominal abscesses are known to present as PUO. Tuberculosis of the spine presenting as psoas abscess is more commonly seen than reported. India has a high incidence of tuberculosis. However, psoas abscess may be due to varied reasons and empirical treatment may not be justifiable. We report the following case to exemplify the same.

Case History
A 37 yr old male farmer presented with history of low grade fever and low back pain for one month. With these complaints, he was evaluated by his physician. Haemogram and ESR were normal. Chest X-ray was unremarkable. CT scan of abdomen (Figure 1) showed collapse of third lumbar vertebra with large paravertebral and psoas abscess with bilateral sacroilitis. He was considered to have Koch’s spine and was started on rifampicin, isoniazid, pyrazinamide and ethambutol. After 3 weeks, the patient reported back with recurrent vomiting and was re-evaluated. He was found to have renal dysfunction (Serum creatinine 6.2 mg/dl). He was referred to our institute for the management of renal failure. There was history of weight loss of 6

due to previous BCG vaccination. Latent TB infection is considered for any BCG vaccinated person when skin test is 10 mm or greater and was in contact with TB infected person or born or lived in a high TB prevalent country or continually exposed to population where TB prevalence is high. With this background Anti TB Drug administration was justified and further supported by symptomatic improvement of this patient.¹⁴

Anti-TB drugs (ATD) along with steroids have been used by authors across the Indian subcontinent in treating TA with fever and constitutional symptoms, especially if exposure to TB can be documented.¹⁵ The European League Against Rheumatism (EULAR) recommends initial high doses of glucocorticoids for disease control and an immunosuppressive agent (methotrexate, cyclophosphamide, azathioprine or mycophenolate mofetil) as an adjunctive therapy.¹⁶

Conclusion
The purpose of documenting this case was to highlight the extensive involvement of the aorta (Type V), the variety of vascular changes that we found in a single patient (Ishikawa Group 4) and the strong causal association our patient had with a tubercular etiology. More importantly, this case possibly redefines the role of ATD in all patients diagnosed with TA in the Indian subcontinent.

References
kg in the past one month. He also had severe anorexia and malaise. There was no significant past history. Clinical examination was unremarkable. Evaluation showed hemoglobin of 9.1 gm/dl, with leukocyte count being 7800 cells/cumm. Other results were as follows: blood urea nitrogen-180mg/dl, creatinine 7.5mg/dl, ESR 36mm/hour, protein 8.0mg/dl, albumin 3.6 mg/dl, calcium 10.0mg/dl. His urine analysis had trace albuminuria and bland sediments. 24 hour urine protein was 1.7gm. Ultrasound of the abdomen was done, which revealed bilateral normal sized kidneys, and heterogeneous collection over psosas muscle. CT reconfirmed the findings of the first scan done elsewhere. Ultrasound guided aspiration of the psosas collection was done. The cytology smear showed atypical plasma cells (Figure 2). Bone marrow biopsy was reported to be multiple myeloma. Free light chain assay proved it to be a kappa light chain myeloma. Immunofixation electrophoresis showed it to be of IgG origin. He was having cast nephropathy on renal biopsy. He was treated with 5 sessions of plasmapheresis and hemodialysis. He was given bortezomib and dexamethasone based chemotherapy. His urine output improved to 1.2-1.5 liter per day from 100-300 ml per day. He remained dialysis dependent. He had a refractory disease and died within eleven months of diagnosis.

Discussion

In the Indian subcontinent, tuberculosis is very common. With a young farmer presenting with these complaints, the probable diagnoses that need to be considered are tuberculosis, brucellosis, and psosas abscess. Psosas abscess can be due to bacterial, fungal, tubercular, polymicrobial. It can be primary or secondary (as in spinal tuberculosis, ruptured ceacum, genitourinary infection). Tuberculosis of the spine was a strong suspicion in this patient. However, the odd feature was advanced renal failure, with oligoanuria. Osteoarticular brucellosis is the most common presentation of systemic brucellosis. Lumbar spine is the most commonly affected area. Rifampicin, being active against Brucella species, can give the response and could conceal the disease. However, for brucellosis, it is usually used for duration of 6-8 weeks only. He was evaluated without any prejudice and was diagnosed to have multiple myeloma. Treating empirically in the initial period missed the opportunity for a correct and timely diagnosis in this patient.

The exact incidence of multiple myeloma in India is not known. The median age of Indian patients presenting with myeloma is 55 years, a decade less than that in the USA. India has the lowest incidence in Asian countries. The incidence of multiple myeloma in patients younger than forty years is only 2%.

Myeloma can involve gastrointestinal tract, Pleura, Testes, Skin, Peritoneum, Liver, Endocrine Organs, Lymph nodes. Unless there is evidence of any specific disease, in the larger interest of the patient, it is better to follow the age old principle, “culture what you biopsy and biopsy what you culture”. In this patient, aspirate was negative for acid fast bacilli. Bacterial culture of the aspirate was negative. Fungal and mycobacterial cultures were reported to be negative later on. The cells were confirmed to be of myeloid lineage by immunohistochemistry. He developed severe anemia later on and remained transfusion dependent. Though multiple myeloma was not suspected by us initially, methodical evaluation led us to the diagnosis.

Tuberculosis of spine presenting in a manner similar to our patient, in patients of multiple myeloma is reported. A rare case of anaplastic multiple myeloma affecting hip and thigh muscles in a known case of multiple myeloma, after an intramedullary nailing of an impending femoral fracture, is also reported. A patient with known multiple myeloma on chemotheraphy, having a relapse in the form of psosas abscess is reported. But the current presentation does not seem to be reported before. We presume, it may be underreported, as many cases of paraspinal abscesses with spine involvement, are usually empirically treated in clinical practice with no documentation on etiology or follow up or prognosis.

Conclusion

To conclude, we report a case of anaplastic myeloma with extramedullary extension into psosas muscle. Multiple myeloma has many facets and needs to be considered while evaluating relevant cases. Methodological evaluation is needed, rather than treating with intuition.

References

Alexia without Agraphia-report of Five Cases and Review of Literature

Sheetal S¹, Robert Mathew², Byju P³

Abstract
Alexia without agraphia (also called pure alexia or word blindness) was the first of the disconnection syndromes to be described. It results from the loss of visual input to the language area without involvement of the language area. The most common cause is occlusion of the left posterior cerebral artery with involvement of left occipital cortex and the splenium of corpus callosum. However, it can also be caused by any lesion affecting the splenium of corpus callosum disrupting the white matter tracts from the left visual cortex to the angular gyrus. We hereby describe five cases of alexia without agraphia, of which three are due to involvement of the left occipital cortex and splenium, and two are due to involvement of the splenium of corpus callosum alone.

Introduction
Alexia without agraphia or pure word blindness is one of the classic disconnection syndromes.¹ Patients are unable to read (even words that they have just written) but retain the ability to write. This was first described by Dejerine in 1892.²³ This disorder results from the loss of visual input to the language area without involvement of the language area or output from the language area to the motor cortex.

The most common causative lesion is a stroke in the territory of left posterior cerebral artery with infarction of the medial occipital lobe, splenium of the corpus callosum and often the medial temporal lobe.³⁴

We hereby report 5 cases of alexia without agraphia, all resulting due to left posterior cerebral artery infarct.

Case 1
A 77 year old right handed male, with long standing history of type 2 diabetes mellitus, presented to us with complaints of acute onset of blurring of vision in both eyes, associated with headache and vomiting. On examination, he was conscious, oriented. His word output was normal, repetition and comprehension was intact, he could write normally, but could not read. He could not read the words that he had just written. He had impairment in recent memory. Examination of the cranial nerves revealed a right homonymous hemianopia. He had no motor weakness or cerebellar signs. MRI brain was done and it showed T2/FLAIR hyperintensities with diffusion restriction in the left occipital lobe and splenium of corpus callosum (Figures 1, 2), suggestive of acute infarct. Hence the diagnosis of alexia without agraphia due to a left posterior cerebral artery infarct was made. He was started on antiplatelets and statins. On follow up at 1 month, he continued to have alexia without agraphia.

Case 2
A 64 year old right handed male, with history of type 2 diabetes mellitus and ischemic heart disease developed acute onset of vertigo, vomiting and blurring of vision both eyes. On examination, he was conscious, oriented. He had impairment in short term memory. His word output, repetition and comprehension was normal. He had difficulty in naming objects, he could write but he couldn’t read even what was just written by him. He had difficulty in identifying and matching colours. He had no motor weakness.

MRI brain showed T2 and FLAIR hyperintensities in the left occipital region and splenium of corpus callosum (Figures 3, 4). On follow up his symptoms were persisting.

Fig. 1: FLAIR hyperintensities in the left occipital lobe and splenium of corpus callosum

Fig. 2: Diffusion restriction in the left occipital lobe and splenium of corpus callosum

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Received: 10.05.2016; Accepted: 04.04.2019
Case 3

A 63 year old right handed female, hypertensive, initially visited the ophthalmology out patient department with complaints of blurring of vision of both eyes, from where he was referred to us. On examination, she was conscious, oriented, had a blood pressure of 180/110 mm of Hg. She had difficulty in naming colours. She could write normally but could not read, suggestive of alexia without agraphia. Her other language functions including word output repetition and comprehension was normal. A CT brain revealed infarct involving the splenium of corpus callosum (Figure 5). On follow up she had persistence of alexia without agraphia.

Case 4

A 50 year old right handed male, hypertensive, diabetic, presented to us with inability to read the morning newspaper, though he had no difficulty in seeing objects. On examination, he was conscious, oriented, had a blood pressure of 140/90 mm of Hg. He could not read, though could write normally, suggestive of alexia without agraphia. His other language functions including word output repetition and comprehension was normal. A MRI brain revealed infarct involving the the splenium of corpus callosum on the left side (Figures 6, 7, 8). On follow up he had persistence of alexia without agraphia.

Case 5

A 75 year old right handed male, smoker, with no co morbidities, presented to us with complaints of acute onset of headache and vomiting, and difficulty in seeing objects on the right side. On examination, he was conscious, oriented. His word output was normal, repetition and comprehension was intact, and he had difficulty in naming objects. He could write normally, but could not read. Examination of the cranial nerves revealed a right homonymous hemianopia. He had no motor weakness. CT brain showed a hypodensity in the left occipital lobe and splenium of corpus callosum (Figure 9) suggestive of acute infarct.
Discussion

Pure alexia without agraphia or pure word blindness is a disorder in which the patient can write but cannot read their own writing. Alexia without agraphia is a rare but “classic” disconnection syndrome. It was Dejerine, a French neurologist, who described this syndrome. He was the first to describe a patient with this syndrome, whose autopsy revealed an infarct of the left posterior cerebral artery territory involving the splenium of the corpus callosum and the medial portion of the left occipital lobe. He concluded that it is a disconnection syndrome which disrupts the visual input from the occipital lobes to the dominant angular gyrus, without involvement of the language area as such.

There are two theories in the pathogenesis of this syndrome. The dominant angular gyrus is located in the inferior parietal lobule of the cerebral hemisphere, usually the left, and is involved in phoneme processing in language comprehension and phoneme production for repetition and speech. It receives direct input from the left visual cortex. Input from the right visual cortex reaches the left angular gyrus through the splenium of the corpus callosum (Figure 10). Hence, in a lesion involving the occipital lobe and the splenium, vision (the right visual cortex) and language (in the form of speech and writing) are spared, but the patient is unable to read, as visual information cannot be transmitted to the language area. In the reported cases of alexia without agraphia, infarction in the distribution of the left posterior cerebral artery (PCA) is the most common pathologic process. Since the visual cortex is supplied by the posterior cerebral artery, infarction of this area results in a right homonymous hemianopia, which is usually associated with this syndrome. There have been rare reports of alexia without agraphia not associated with right homonymous hemianopia. This brings in the second theory - a single lesion proximal to the language area (with sparing of the left visual cortex) affecting the fiber tracts from both visual cortices can explain these symptoms (Figure 11).

In our third and fourth case, our patients had alexia without agraphia, not accompanied by right homonymous hemianopia. MRI brain in these patients revealed an infarct adjacent to the splenium of corpus callosum, without involvement of the left occipital lobe, fitting with the second theory of this syndrome. All the other patients had infarct involving the left occipital cortex and the splenium of the corpus callosum.

References


Hemophagocytic Lymphohistiocytosis in a Patient of Scrub Typhus

Sudhir Mehta1, Nidhi Sharma2, Laxmi Kant Goyal3, Sandhya Gulati4, Tara Chand5, Om Prakash Nag5, Sahdev Patel6

Abstract

Hemophagocytic lymphohistiocytosis (HLH) is a rare but aggressive and potentially fatal condition characterized by excessive immune activation. It can occur as primary/familial and secondary/sporadic/ acquired form. Infections can play a role as triggers in the secondary form of HLH. A case of HLH associated with scrub typhus is being reported here. Such association of scrub typhus and HLH is rare.

Case Report

An 18 years old male youth was admitted in medical ward with complaint of high grade continuous fever since 10 days. There was

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare but aggressive and potentially fatal condition characterized by excessive immune activation. It has variable clinical presentation and lack specific symptoms and signs but prompt initiation of treatment is essential for the survival of affected patients. It can occur as primary/ familial and secondary/sporadic/ acquired form. Infections can play a role as triggers in the secondary form of HPLS. A case of HLH associated with scrub typhus is being reported here. Such association of scrub typhus and HLH is rare.

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Received: 26.07.2016; Accepted: 24.04.2019
History of cough without sputum production since 3 days along with yellow discoloration of eyes. On the day of admission in hospital, he also developed petechiae over the limbs and trunk. There was no past history of such illness/drugs ingestion/any significant medical illness. On examination he was conscious, cooperative. His vitals were pulse 108/minute, blood pressure 114/76 mm of Hg, temperature 102°F, respiratory rate 22/minute with thoraco-abdominal respiration and oxygen saturation was 94% at room air. Clinical examination revealed tender hepatomegaly and splenomegaly (2 cm below costal margin) along with fine crepitations at base of right lung. Lymph nodes were not palpable. Petechiae were present on trunk and all four limbs.

Blood report revealed Hb-7.3 gm%, TLC-34.04 thousand/mm3, N93L05, platelets-16,000/mm3, PCV 22.1%, ESR-33 mm/1st hour. Peripheral blood smear showed leukocytosis with neutrophilia, anisocytosis, microcytic-hypochromic anaemia with markedly reduced platelets. Few lymphocytes, monocytes and atypical cells were also found on blood film. Random blood sugar was 97 mg/dl, serum urea was 130 mg/dl and serum creatinine was 1.76 mg/dl. Liver function test revealed serum bilirubin 6.9 mg/dl, direct bilirubin-3.3 mg/dl, AST-49 U/L, ALT-19 U/L, serum alkaline phosphate-217 IU/L, albumin - 2 gm/dl, globulin-3.3 gm/dl. Blood for widal test, malaria dual antigen, dengue serology (NS1 antigen, IgG and IgM antibodies), leptospira IgM, HIV, Hepatitis B Surface Antigen and anti HCV were negative. Test for scrub typhus (Igm ELISA) was positive. USG abdomen showed hepatosplenomegaly with minimal ascites. Serum Ferritin was 1600 ng/ml and serum triglyceride was 293 mg/dL. Chest X-ray revealed bilateral non-homogenous opacities in middle and lower zones. The patient was put on oxygen, given intravenous fluids, antibiotics (oral doxycycline and IV azithromycin) and platelet transfusions. The platelet count and hemoglobin failed to increase after 5 days of antibiotics. Then bone marrow aspiration and biopsy were done to rule out any hematological malignancy. The bone marrow revealed hyper cellular marrow with phagocytic histiocytes ingesting blood cells indicating HLH (Figure 1).

Discussion

Hemophagocytic lymphohistiocytosis (HLH) is a rare but aggressive and potentially fatal condition characterized by excessive immune activation.1 HLH presents with multiorgan involvement manifesting as fever, hepatosplenomegaly, lymphadenopathy, blood cytopenias, altered mental status, elevated serum ferritin and abnormal liver functions.2 Many patients with HLH have a predisposing genetic defect, and/or an immunologic trigger, which can include infection, malignancy, rheumatologic disorder (i.e., juvenile idiopathic arthritis) or disorders associated with immune dysregulation. Infections can play a role as triggers in the secondary form of HLH. HLH associated infections includes Epstein Barr virus, cytomegalovirus, parvovirus, herpes simplex virus, varicella zoster virus, measles virus, human herpes virus8, H1N1 influenza virus, and HIV.3,4

The diagnosis of secondary HLH is based on fulfilling five of eight diagnostic criteria. These 8 criteria include 1. Fever ≥38.5°C, 2. Splenomegaly, 3. Peripheral blood cytopenia, with at least two of the following: hemoglobin <9 g/dL (for infants <4 weeks, hemoglobin <10 g/dL); platelets <1Lac/µL; absolute neutrophil count <1000/µL, 4. Hypertriglyceridemia (fasting triglycerides >250 mg/dL) and/or hypofibrinogenemia (fibriogen <150 mg/dL), 5. Hemophagocytosis in bone marrow, spleen, lymph node, or liver, 6. Low or absent NK cell activity, 7. Ferritin >500 ng/mL, 8. Elevated soluble CD25 >2400 U/mL.5

When a diagnosis of secondary HLH is established, patient should be evaluated for a possible infectious trigger/immunological/rheumatologic or malignant disease. In our case the patient was positive for scrub typhus. Scrub typhus is a rickettsial disease, caused by Orientia tsutsugamushi. The pathognomic finding in scrub typhus, a necrotic eschar at the inoculating site of the mite, is rarely seen in south East Asia region including Indian subcontinent.6 There are only few case reports showing scrub typhus as a trigger for HLH. The peculiar finding in our case was leucocytosis which is seen in 25% cases of HLH and the same has not been reported in case reports of scrub typhus with secondary HLH. Association of scrub typhus and HPLS in adult patient is rare.7

HLH should be suspected in non-responding cases of Scrub typhus associated with persistent cytopenias/leucocytosis despite optimal treatment of scrub typhus.

References

Movement Disorder and Epilepsy in Subependymal Nodular Heterotopia

Anurag Lohmror¹, Richa Choudhary¹

Abstract

Context: Subependymal nodular heterotopia is a cortical development malformation that is commonly associated with refractory epilepsy. Patients with heterotopia show a wide spectrum of clinical manifestations, from being asymptomatic to presenting with intractable seizures and intellectual impairment.

Case Report: We report a case of refractory epilepsy with normal intelligence, having bilateral subependymal heterotopic nodules in brain, presenting to us with a movement disorder in the form of myoclonus of bilateral lower limbs which is an unusual manifestation of gray matter heterotopias.

Conclusion: Though rare, gray matter heterotopias may present as movement disorder and should be considered in differential diagnosis while work up of movement disorders.

Introduction

Subependymal nodular heterotopias (SNH) are one of the most frequent malformations of cortical development.¹Gray matter heterotopias are best divided into three categories: subependymal, sub cortical, and band heterotopia. According to the classification system developed by Barkovich et al, updated in 2012, SNH are classified as malformations due to abnormal neuronal migration (Group II).² The main presenting feature in most patients with nodular heterotopias is focal drug resistant epilepsy with onset in second decade of life; development and neurological examination is otherwise normal. Here, we present a patient with generalized epilepsy and movement disorder in the form of myoclonus, whose MRI was consistent with bilateral subependymal nodular heterotopia.

Case History

A 19 year old female with a previous history of convulsions for last nine years presented to our department with myoclonus of bilateral lower limbs for three months. The onset of convulsions was at the age of ten years occurring with a frequency of 2 to 3 episodes per month. The convulsions were preceded by aura, described by the patient as heaviness in head, and were generalized tonic clonic in nature, each episode lasting for 1 to 2 minutes followed by 15 to 20 minutes of post ictal confusion. Medically she was initially treated with valproic acid with partial success. Clobazam and levetiracetam were added to control the convulsions and the family reported improvement. Her perinatal history was unremarkable and developmental milestones were achieved at appropriate ages. Although she was unable to complete her schooling after primary school level due to her medical condition, on examination her intellectual ability was within normal range. There was no family history of seizures. Neurological examination was unremarkable except for the presence of myoclonus in bilateral lower limbs. No evidence of neurocutaneous markers was present.

Investigations revealed normal haemogram and serum biochemistry. Concomitant congenital abnormality was present during screening for associated anomalies in the form of left ectopic (left iliac fossa), malrotated and small sized kidney.

Magnetic Resonance Imaging (MRI) of the brain was performed using spin echo and fast spin echo pulse sequences. Serial T1 and T2 weighted images were obtained in the sagittal,coronal and axial planes. Special fast FLAIR images were also obtained. The study revealed nodular lesions isointense to gray matter on all pulse sequences seen along lateral margins of bodies, frontal and occipital horns of bilateral lateral ventricles consistent with subependymal gray matter heterotopias (Figure 1).

No abnormal enhancement on contrast administration was seen. This allows these nodules to be distinguished from the subependymal nodules of tuberous sclerosis that do not follow gray matter signal, and enhance after contrast administration. Electroencephalogram (EEG) was suggestive of generalized epileptiform discharges.

Fig. 1: Subependymal Heterotopia- Magnetic Resonance images (a) T1-weighted axial section showing multiple subependymal nodules (arrows), isointense to cortical gray matter, symmetrically lining the lateral walls of the lateral ventricles; (b) T2- weighted coronal section demonstrating heterotopic nodules along the paratrigonal region of both ventricles; (c) Axial inversion-recovery magnetic resonance (MR) image showing bilateral nodules indenting the walls of ventricles (arrows)

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Received: 28.04.2016, Accepted: 04.04.2019
Subependymal Nodular Heterotopia (SNH) was initially thought to be a neural migration disorder characterized by nodules of neurons due to arrested migration or failure of neuroblasts to undergo apoptosis but according to recent research, neuroependymal injury, rather than an intrinsic motility defect of the cell, is thought to be an important pathogenic factor in the development of SNHs. The denuded ventricular epithelium in periventricular/subependymal nodular heterotopia may cause disengagement of radial glia, resulting in an inability of young neurons to migrate away. The subependymal nodules are the most common form of grey matter heterotopias, which are located close together and form irregular lumps adjacent to the lateral ventricles, bilaterally or unilaterally.

The true prevalence of nodular heterotopias in the general population and in patients with epilepsy is unknown. Subependymal heterotopias usually present sporadically, however some cases are familial and demonstrate an X-linked pattern of inheritance. Mutations in FILAMIN 1 gene, located on chromosome Xq28, have been associated with both sporadic and familial SNH.

Clinically, patients with subependymal heterotopias not associated with other types of cortical or cerebral malformations generally have normal development and motor skills. In a long term follow-up, monitoring the course of epilepsy in 16 SNH patients d’Orsi et al found that isolated SNH patients without any associated cortical or cerebral malformation have a comparatively “benign” course with seizures beginning during the second decade of life and rare in frequency at onset. The seizure type in these patients is usually partial with secondary generalization and drug responsive, without mental retardation. EEG may be normal or with focal abnormalities. During life, seizures may temporarily increase, but without reaching a high frequency and usually disappear or become very rare. A kidney malformation (ectopia) was evident in one of their patients. In the present case, a similar congenital anomaly in the form of left ectopic (left iliac fossa) and malformed kidney was present.

In our case, the subject had onset of seizures in her second decade of life which were partially controlled and myoclonus of bilateral lower limbs. This was similar to two cases reported by J. P. Mullin et al in pediatric age group, both patients manifested as movement disorders as presenting features of heterotopias. Both patients experienced significant improvements following resection of their heterotopias.

MRI is far more sensitive than CT in the detection of subependymal heterotopias. On MRI subependymal heterotopias appear as ovoid lesions within the subependymal region. Neither perilesional edema nor contrast enhancement is seen. Donkol RH et al reported three types of heterotopia detected by MRI in a study of 20 patients (female to male ratio14:6), all having a history of seizures. SNH was the commonest type, followed by Subcortical Heterotopia, while Band Heterotopia was the least common type. The heterotopic tissue was isointense with gray matter on all MR pulse sequences. Several studies revealed that most of the heterotopic nodules experience epileptic activity of their own accord at seizure onset, which is synchronous with the overlying neocortex or ipsilateral hippocampus. The heterotopia can generate not only normal EEG activity but also interictal and ictal epileptic discharges, usually synchronous with, but sometimes independent from the surrounding allo or neocortex.

In conclusion, heterotopias are a rare subgroup of cortical malformations characterized by abnormal neuronal migration, usually presenting as refractory epilepsy. In literature very few cases of heterotopic gray matter associated with movement disorders have been reported. Hence, the case above is reported to emphasize the unusual manifestation of subependymal nodular heterotopias as movement disorders.

References


Neuro-Chikungunya: Acute Transverse Myelopathy Associated with Chikungunya Virus Infection

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Abstract
Chikungunya is an arboviral infection caused by Chikungunya virus, an RNA virus from Togaviridae family.¹ The disease manifests as fever, rash and characteristically with arthralgia.² Chikungunya is strongly believed to have neurotropism but has not been well studied like other neurotropic arboviruses.² Encephalitis appears to represent the most common clinical manifestation³ and occurs either simultaneously or within few days of onset of systemic symptoms, during the period of viremia. A delay of more than two weeks has been reported with other complications like myelitis, Guillian Barre syndrome and optic neuritis. This case describes the clinical, serological, neuroimaging and CSF findings of Chikungunya induced acute transverse myelitis in a 13 years old male patient who responded to steroid treatment. It is a relatively unknown and very rare complication of Chikungunya virus infection during outbreak of Chikungunya infection in September 2016.

Introduction
Chikungunya virus is an insect-borne (Aedes mosquito) virus of the genus Alphavirus and the family Togaviridae.¹ The word Chikungunya means, “become twisted” in the Kimakonde language, of ethnic group in southeastern Tanzania and Northern Mozambique. After a average incubation period of 2 to 4 days (2 to 12 days) the disease manifests, without prodromata, with typical features of fever, rash and arthralgia.²³⁴ Children are among the high risk group for severe manifestations of the disease and some clinical features in this group are distinct from those seen in adults. Chikungunya virus is considered primarily a non-neurotropic virus but neurological complication like meningo-encephalitis, myeloneuropathy, Guillian Barre syndrome, optic neuritis⁶ etc. have been reported. A history of fever, polyarthralgia, and/ or rash in patients with neurologic symptoms may be the first clues to neuro-Chikungunya. Clinical findings or neuroimaging suggestive of demyelination process may lead to proper selection of appropriate serodiagnostic tests.

Case Report
A 13 year old school going male from Aligarh, Uttar Pradesh, presented with chief complaint of inability to walk since 5 days. There was history of high grade fever which lasted for 2 days, associated with arthralgia and myalgia, 10 days before the development of paraparesis. He had associated history of urinary retention, constipation, decreased sensation for pain, touch and temperature below T8 spinal segment level. There was no history of recent vaccination, trauma to spine/limbs, contact with tuberculosis patient or anti-tuberculous therapy in past. Similarly there was no history of rash, bleed from any site, malena, joint swelling, respiratory problem or pedal edema. He had no complaint of blurred vision, diplopia, facial nerve palsy features, nasal regurgitation or features suggestive of any other cranial nerve involvement. There was no history suggestive of nystagmus, slurred speech, altered sensorium, seizures, ataxia, headache, vomiting.

On clinical evaluation, patient was conscious and alert. Further physical examination revealed hypertonia and brisk deep tendon reflexes in lower limbs. Power was grade [0/5] in bilateral lower extremities, in both proximal and distal segment. Plantar response was extensor bilaterally, absent abdominal reflex and ankle clonus were present in both lower limbs. Tone, power and all deep tendon reflex were normal in upper limbs. Respiratory, Cardiiovascular and Abdominal examination were unremarkable.

Laboratory results revealed, Hb 11.7gm/dl, ESR-20mm, TLC-4520/ cumm, Platelet count- 92000/cumm, B. Urea- 39mg/dl, S. Creatinine- 0.4mg/ dl, Serum Na+/K+-138/4.3 mEq/L, S.Bilirubin- 0.8mg/dl, SGOT/SGPT-60/50u/l, ALP- 145u/l, S.Albumin-3.3gm/dl, S.Globulin- 2.7gm/dl, Serum Calcium/Phosphate- 8.3/3.5mg/dl. HIV(I and II), Hepatitis B and Hepatitis C serology was negative. Dengue serology (IgG and IgM), NS1 Antigen, Malaria serology (and antigen), Peripheral smear for malaria parasite, and Widal test were discovered to be negative. IgM chikungunya Serology by ELISA was positive and chikungunya PCR was negative in serum sample. Autoimmune marker Antinuclear antibody, Rheumatoid factor, Anticardiolipin antibody and anti dsDNA were negative. Serum NMO Antibody against water channel protein aquaporin-4 was negative. Optic neuritis was ruled out on basis of normal visual evoked potential and absent relative afferent papillary defect. Fundus examination was normal. MRI Brain showed nonspecific demyelinating foci in bilateral frontoparietal subcortical white matter with no restricted diffusion or post contrast enhancement, largest in the left parasagittal parietal white matter.

MRI Spine showed long segment cross sectional altered intramedullary signal in cord from C5-C6 disc to D8 body (Figure 1). Another intramedullary hyperintense lesion was found opposite C5 vertebrae and C2-C3 vertebrae in posterior
Chikungunya virus, a RNA Arbovirus which mostly causes self-limiting febrile illness, had its recent outbreak in September 2016 in Delhi and various other states of India. Being associated with morbidity in the form of rheumatic symptoms (joint pains, swelling and stiffness) and rash, chikungunya can infrequently cause neurological sequelae which can be more or less life threatening.

Since 2005, small mutation in the E1 protein of the viral envelop have been considered as a major explanation of disease having varied complications and its expansion in South-east Asian countries. The exact pathophysiology of neurological involvement in Chikungunya infection has not been established. There are reports of association of neurological involvement in animal experimental studies, strongly points toward possible neurotropism of this virus.

Although spectrum of neurological manifestations ranging from encephalitis, Guillain Barre syndrome, external ophthalmoplegia, sensorineural deafness etc. have been reported but Acute transverse myelitis is a rare complication of chikungunya. The presence of Chikungunya virus in the CSF establishes chikungunya as the cause of acute transverse myelitis on this case.

Our patient was confirmed as having Chikungunya infection on the basis of detection of CHIK IgM in serum and positive real time-PCR in CSF sample. The negative result of CSF reverse transcriptase PCR (RT-PCR) assay for CHIKV RNA was not surprising because of late presentation of the patient and lumber puncture for CSF result was done after 20 days of symptoms onset. The time lapse between acute Chikungunya infection and the onset of myelopathic sequelae, and response to steroid, suggests an immune mediated phenomenon rather than direct activity of the virus itself. We chose to rely on RT-PCR detection of the virus to diagnose CHIKV infection rather than testing for IgM antibodies, which may persist for several months after infection and could reflect coincidental infection rather than an acute infection. In summary, during CHIKV outbreaks, clinicians should consider that CHIKV may be a likely cause of CNS infections among children.

This case emphasizes the fact that studies are scarce that report transverse myelitis confirmed with Chikungunya PCR. There is further paucity of literature on such patients showing response with steroids. Thus patients with chikungunya infection should be followed up for possible neurological complications.

Chikungunya is expanding its territory and is posing a threat to non-immune population in many countries. Therefore, physicians are expected to see more cases of Chikungunya and thus Neuro-chikungunya in the future.

References
An Unusual Presentation of Weil’s Disease

Souren Pal

Abstract

Leptospirosis is a potentially fatal disease which can cause multi-organ dysfunction. It can have different rare presentations. Acute pancreatitis is one such rare gastrointestinal manifestation which present as an acute abdomen. Simultaneous presence of features of both acute pancreatitis and acute hyponatremia in a case of Weil’s disease characterised by combination of jaundice, acute kidney injury, hypotension and hemorrhagic manifestation is very rare.

Introduction

Leptospirosis, potentially fatal, re-emerging zoonotic disease globally, is caused by spirochetes of genus Leptospira. The clinical phenotype of infection includes subclinical infection, an undifferentiated febrile illness and the most serious form known as Weil’s disease characterised by variable combinations of jaundice, acute kidney injury, hypotension and hemorrhage. Pancreatitis as a secondary complication of the disease is very rare and only a few cases have been reported.

Case Report

A 57 year old male patient from rural area admitted to hospital in August with high grade continuous fever with jaundice, myalgia and redness of right eye for seven days, cough, hemoptysis, decreased urine output for three days, diffuse pain abdomen with nausea and vomiting for two days and drowsiness for last 24 hours. He was non-diabetic, nonhypertensive, non-smoker and nonalcoholic. He had no history of contact with jaundiced persons, blood transfusions and drug abuse.

On examination he had BP 80/40 mm of Hg, pulse 110/min and regular, GCS 11/15 and his sclera were icteric with subconjunctival hemorrhage (Figure 1). There was marked, rebound tenderness with guarding in his whole abdomen with sluggish peristaltic sounds. Chest was clear with bilateral vesicular breath sound except on right apical area where it was diminished.

Routine blood parameters done serially are shown in the Table 1. Malaria parasite dual antigen test by immunochromatographic assay of pLDH and HRP-2, IgM Dengue in serum by MAC ELISA method, HBsAg, antiHCV, IgM anti HAV, IgM anti HEV, HIV were negative. ABG analysis was almost normal except for low oxygen saturation (85%).

Treatment was started with IV fluid along with hypertonic saline, antipyretics and moist oxygen. Considering low platelet count, four units of platelet were transfused. Chest X-ray was non-contributory. Due to high index of suspicion, serum sample for IgM Leptospira was sent. Patient regained consciousness on Day 3 after partial correction of hyponatremia but hemoptysis, icterus, pain abdomen, decreased urine output persisted. Results of IgM Leptospira came on Day 3 and it was 85.0 U/mL (Negative <15.0, Intermediate 15.0-20.0, Positive > 20.0). Injection ceftriaxone 1gm IV once daily was started. CECT Scan of abdomen, done after normalisation of urine output on day 7, showed bulky pancreas (Figure 2) hence confirmed the presence of acute pancreatitis. HRCT Scan of thorax (Figure 3) revealed focal ground glass opacity in right apical and anterior segment of upper lobe possibly of pulmonary haemorrhage. Subsequent sputum examination was negative for acid fast bacilli. So a diagnosis of acute

Table 1: Routine biochemical tests on day 1, day 3, day 7 & day 14

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb%</td>
<td>11.8</td>
<td>11.9</td>
<td>11.9</td>
<td>12.1</td>
</tr>
<tr>
<td>TLC (/cmm)</td>
<td>15900</td>
<td>21700</td>
<td>11200</td>
<td>7400</td>
</tr>
<tr>
<td>DC</td>
<td>N94L2M2E2</td>
<td>N91L5E4</td>
<td>N80L14E4M2</td>
<td>N66L28M2E4</td>
</tr>
<tr>
<td>Platelet Count (Lac/cmm)</td>
<td>0.20</td>
<td>0.50</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>14.7</td>
<td>30.5</td>
<td>8.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dl)</td>
<td>7.4</td>
<td>12.3</td>
<td>6.8</td>
<td>1.3</td>
</tr>
<tr>
<td>SGOT (U/L)</td>
<td>82</td>
<td>61</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>SGPT (U/L)</td>
<td>27</td>
<td>42</td>
<td>37</td>
<td>60</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>72</td>
<td>97</td>
<td>183</td>
<td>123</td>
</tr>
<tr>
<td>Total protein (gm/dl)</td>
<td>4.5</td>
<td>4.7</td>
<td>4.8</td>
<td>5.1</td>
</tr>
<tr>
<td>Albumin (gm/dl)</td>
<td>2.6</td>
<td>2.6</td>
<td>2.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Amylase (U/L)</td>
<td>984</td>
<td>1180</td>
<td>986</td>
<td>595</td>
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<tr>
<td>Lipase (U/L)</td>
<td>1012</td>
<td>1310</td>
<td>1194</td>
<td>183</td>
</tr>
<tr>
<td>Na+ (meq/L)</td>
<td>110</td>
<td>120</td>
<td>141</td>
<td>146</td>
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<td>K+ (meq/L)</td>
<td>3.1</td>
<td>3.2</td>
<td>4.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>66</td>
<td>118</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>5.1</td>
<td>4.9</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Sugar (mg/dl)</td>
<td>118</td>
<td>56</td>
<td>88</td>
<td>109</td>
</tr>
<tr>
<td>Urine RBC (HPF)</td>
<td>Plenty</td>
<td>Plenty</td>
<td>10-20</td>
<td>5-10</td>
</tr>
<tr>
<td>Urine protein</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NIL</td>
</tr>
<tr>
<td>P-time (sec) &amp; INR</td>
<td>14.3 &amp; 1.2</td>
<td>14.2 &amp; 1.2</td>
<td>13.6 &amp; 1.2</td>
<td>13.6 &amp; 1.2</td>
</tr>
<tr>
<td>APTT (sec) (Ref Int:22.6-35)</td>
<td>25.6</td>
<td>25.8</td>
<td>26</td>
<td>25.6</td>
</tr>
</tbody>
</table>

Fig. 1: Subconjunctival haemorrhage in icteric right eye and only icterus in left eye
leptospirosis complicated by acute pancreatitis, acute renal failure, acute hyponatremia with bleeding diathesis was confirmed.

Pain abdomen, fever and haemoptysis was subsided on day 10. Jaundice was gradually decreased. On day 14 patient was discharged. On first follow up 2 weeks after discharge patient was completely anicteric.

Discussion

Pathogenesis of organ dysfunction in leptospirosis is yet to be fully understood. It is characterised by the development of vasculitis, endothelial damage and inflammatory infiltrates composed of monocyctic cells, plasma cells, histiocytes and neutrophils.

Pancreatitis as a secondary complication of leptospirosis is very rare. Serum amylase may be raised in upto 60% of patients with renal impairment. But in our patient pancreatitis was confirmed by laboratory investigations, imaging study and absence of other common causes of pancreatitis like gall stone, alcoholism or drug intake. CT scan is a gold standard in diagnosis of acute pancreatitis and it has 100% specificity and over 90% sensitivity. Possible mechanism of acute pancreatitis are endothelial damage, inflammatory infiltration, vasculitis of small vessels with ischemic injury leading to activation of proteolytic enzymes and pancreatic auto-digestion. In previously reported fatal cases, pancreatic histopathologic results showed mainly interstitial inflammation with lymphocytic infiltrates, fat necrosis, edema, hemorrhage, congestion and rarely calcification.

Considering the abrupt presentation in a previously healthy person with fever, jaundice and body ache, raised blood urea, creatinine, liver enzymes and bilirubin, amylase and lipase level and all subsiding to normal values with medical treatment; the possibility of acute pancreatitis caused by probable leptospiral infections is to be considered in a background of high titers of Leptospiral IgM antibody.

Hepatic dysfunction in leptospirosis is due to mainly focal periportal cellular necrosis and intrahepatic cholestasis but widespread hepatocellular necrosis is not found.

Pulmonary involvement in leptospirosis occurs in 12% to 67% cases. The severity of pulmonary involvement is unrelated to the liver function. But abnormal radiological findings are found in more than half of patients despite the absence of respiratory symptoms.

Thrombocytopenia is a common finding in leptospirosis, occurring in 40.0-85.6% of this disease. Vasculitis, increased peripheral destruction and decreased thrombocyte production and consumption of thrombocytes have been considered as potential causes of thrombocytopenia. Lengthy disease and acute kidney injury are also the risk factors for thrombocytopenia. The patient described here had acute renal failure as well as thrombocytopenia.

Hyponatremia occurs frequently in tropical diseases as a result of increased levels of antidiuretic hormone, entry of sodium into cells, sodium loss and resetting of osmoreceptors. Tubulointerstitial nephritis is a common clinicopathological finding in leptospirosis. Primary injury of the proximal convoluted tubule is regarded as the hallmark of the kidney in leptospirosis.

Though association of pancreatitis in acute leptospirosis is rare but still reported in various journals. But presentation of acute pancreatitis, acute hyponatremia, thrombocytopenia and haemorrhagic manifestations simultaneously in a case of acute icteric leptospirosis is extremely rare.

Conclusion

Leptospirosis should be considered in the differential diagnosis of acute pancreatitis with jaundice, acute renal failure and dys electrolytemia in endemic areas. Early diagnosis and appropriate treatment is essential.
A Rare Case of Mediastinal Non-seminomatous Germ Cell Tumour with Acute Megakaryocytic Leukaemia

GS Chowdhary¹, Malav Jhala²

Abstract
The most common extragonadal site of Nonseminomatous Germ Cell Tumours is the mediastinum. These are similar to their gonadal counterparts in histology but have a poorer prognosis. The association of mediastinal germ cell tumours with blood borne malignancies has been established in many case reports. However, the association of concomitant mediastinal non seminomatous germ cell tumours with Acute Megakaryocytic Leukaemia is very rare with only 26 cases reported in the last 07 Decades. These patients have a very poor prognosis with only one survivor being reported till present date. AML (M7), a rare variant of Primary AML, has been more commonly associated with non seminomatous germ cell tumours. Here, we report such a rare case of dual malignancy, Non Seminomatous Germ Cell Tumour with AML (M7) which was managed at our centre.

Introduction
The association between mediastinal germ cell tumors and hematological malignancies has been known to the medical community for more than 2 decades.¹ ² This association was established as a clinical entity by Nichols et al. in 1990. The association is rare and has been described mostly in case reports and case series for more than 20 years.³ ⁴ Our extensive literature review has revealed that there are only 26 reported cases of such dual malignancies coexisting together since in 1946.

The etiology is different compared to treatment-related leukemia. Acute Megakaryoblastic leukemia, which is rare form of primary AML, is found to be more commonly associated with primary mediastinal non seminomatous germ cell tumours. Here, we report a case of acute megakaryocytic leukemia associated with a nonseminomatous primary mediastinal germ cell tumor whose diagnosis was a challenge.

Fig. 1: Mediastinal biopsy : Hair shafts seen, suggestive of a teratomatous differentiation

Case History
A 30 year old male, serving soldier, resident of Ahmedabad and hailing from Karnakata, presented with a 01 week history of retrosternal pin pricking type of chest pain radiating to the back with acute onset non progressive dyspnea on exertion (MMRC Class II) and episodic dry cough which would aggravate on supine position. There was no history of associated fever, hemoptysis, wheezing episodes, seasonal variation of symptoms. The patient denied history of any addictions, similar episodes in the past or any high risk behaviour. He had no history of associated comorbid illness. His initial general and systemic evaluation was normal with a normal testicular examination. During his initial workup, he was found to have polymorphonuclear leukocytosis (TLC-14,300/cmm) with thrombocytopenia (60,000/cmm) and marginally raised serum LDH levels (234 IU/L) with his Chest Radiograph showing a well defined Radio-opaque mass in the mediastinum to the left with a wavy outline. His contrast enhanced CT Thorax showed an Anterior mediastinal mass lesion (82 x 72 mm in axial plane with 84 mm cranio-caudal course of leptospirosis infection. J Int Med Res 2002; 30:535-540.
Chemotherapy with Daunorubicin BEP regimen followed by Induction Leukemia (AML M7) with 2 cycles of Tumour with Acute Megakaryoblastic as a case of Mediastinal germ cell lineage with normal lymphoid and myeloid series. He was managed as a case of Mediastinal germ cell Tumour with Acute Megakaryoblastic Leukemia (AML M7) with 2 cycles of BEP regimen followed by Induction Chemotherapy with Daunorubicin and Cytosine-Arabinoside (7+3 regimen). However, he developed febrile neutropenia after induction chemotherapy with progressed to septic shock with multiorgan dysfunction. He subsequently succumbed to sepsis after 45 days of diagnosis.

Discussion

The mediastinum is the most common site of primary extragonadal germ cell tumours.\(^7\) One to six percent of all mediastinal tumours are primary malignant germ cell tumours.\(^8\) Extranodal germ cell tumours generally occur in the midline of the body, like the pineal gland, mediastinum and retroperitoneum. The histological characteristics of extranodal germ cell tumours is similar to their testicular counterparts, but have a poorer prognosis.\(^9\) These tumours are closely related to serum tumour markers, especially serum Alfaetoprotein and Beta HCG levels, which aid in the diagnosis of the disease. Our case was a diagnostic challenge as the bone marrow studies were revealed features of Acute Megakaryocytic Leukemia morphologically, but had inconclusive Immuno- Histochemistry and Flow Cytometry on two instances. It was only after a review of the slides was done with the intention to look specifically for Megakaryocytic precursors that the tissue diagnosis was achieved. It was a tricky task to manage this patient as he had persistent thrombocytopenia requiring frequent platelet component therapy in order to initiate chemotherapy. He eventually developed chemotherapy related febrile neutropenia which progressed to sepsis with septic shock and he succumbed to his illness after nearly 10 weeks from the time of first clinical suspicion diagnosis. Our extensive review of literature of the association between non seminomatous mediastinal germ cell tumours and Acute Myelocytic Leukemia revealed a total of 26 such cases reported since 1946. Out of these cases, 26 were males while the sex of 6 was not known. The median age of presentation with this malignancy has been found to be 23 years (15-46 years) with an average time to diagnosis being 09 weeks (2-39 mths) and a median time to death being 06 months. Out of these cases there has been only one survivor reported who underwent allogenic bone marrow transplant. The prognosis of these patients has been found to be poor even after timely diagnosis and initiation of treatment. The review of literature also revealed that most of the cases succumbed to chemotherapy related complications.

Conclusion

To conclude, Mediastinal Non Seminomatous Germ Cell Tumours with Acute Megakaryocytic Leukemia (AML M7) is a rare combination of dual malignancies which affects the young male population and has a poor prognosis.

References

Spontaneous Splenic Rupture in a Case of Infectious Mononucleosis

Suresh MK¹, Sreenath S², Vijay Narayanan H²

Abstract
Infectious Mononucleosis is a common viral illness mainly of adolescent-young adult age group. Spontaneous splenic rupture is a rare but potentially fatal complication of Infectious Mononucleosis occurring in less than 0.5% of the cases. A high index of suspicion especially if abdominal pain develops during Infectious Mononucleosis is very crucial to early diagnosis and intervention in the case of rupture. Here we discuss the case of a 24 year old male with no previous comorbidities and stable vitals who presented with febrile illness of one week duration associated with abdominal discomfort. Even though initial evaluation did not point towards any etiological clues, a CT imaging of the abdomen was opted due to his persistent abdominal symptoms which showed features suggestive of a contained rupture of spleen. The lack of a specific trauma history prompted further workup for an infective etiology and patient was subsequently found to be positive for Epstein Barr Virus antigen and was diagnosed to have Infectious Mononucleosis. Rupture being of lower grades, non-operative management was opted for and patient improved with conservative management over 4-8 weeks with no further complications. We also discuss the internationally accepted grading of splenic injury and the general consensus regarding management of the same. A general search of the available literature showed very few cases of spontaneous splenic rupture in Infectious Mononucleosis being reported especially from India and hence the importance of this case.

Introduction
Infectious Mononucleosis, caused by Epstein Barr Virus, a member of the Herpesviridae family, is a common infection of worldwide significance, with more than 90% individuals having been infected by adulthood.¹ Infectious Mononucleosis most often presents with nonspecific symptoms such as sore throat, malaise, headache and abdominal pain. Most cases are self-limited-one of the most feared complications, though rare and occurring in less than 0.5% of cases, is splenic rupture. Splenic rupture occurs more commonly in male patients and requires a high index of suspicion for early diagnosis.¹

The presentation of splenic injury can vary, and may manifest as abdominal pain, referred left shoulder pain (Kehr’s sign) or hemodynamic instability.¹

Computer-aided tomography (CT) of the abdomen and pelvis with intravenous (IV) contrast is the preferred imaging modality for stable patients with suspected splenic injury, while focused assessment with sonography in trauma (FAST) should be used for unstable patients.²

Due to the overwhelming risk of post splenectomy infection, there has been a shift away from operative treatment of splenic injury. Non-operative management has become the standard of care in hemodynamically stable patients.²

Case Report
A febrile 24 year old male from Thiruvananthapuram who was working in Middle East, presented to the emergency department with chief complaints of fever for 7 days, abdominal discomfort for 3 days. He reported the fever to be high grade associated with chills and rigor. There was no abdominal pain initially but he reported a constant dull aching pain to be present in the left flank region for past 3 days. He also noticed a yellow discoloration of eyes and urine for the past two days. He did not report any complaints of dysuria, altered bowel habits, vomiting, reduced urine output or any bleeding manifestations. He gives no history of any addictions, habituations, significant past medical illnesses or illness running in the family.

Vitals at the time of presentation consisted of a temperature of 38.2°C, pulse rate 100/min regular, respiratory rate 18/min, and blood pressure 114/72 mm of Hg and oxygen saturation 99% on room air. Physical examination findings included an alert 24 year old moderately built male who appeared comfortable and not in acute pain or distress. Bilateral posterior cervical lymph nodes were found to be enlarged with minimal tenderness on palpation. His abdomen was soft, nondistended and a tenderness was noted in the left hypochondrium. No hepatosplenomegaly was appreciated but the examination was limited due to voluntary guarding. Traube’s space appeared to be dull on percussion.

Pertinent results among initial diagnostic testing consisted of an elevated total leucocyte count of 13,560, thrombocytopenia 80,000, peripheral smear showing moderate thrombocytopenia and elevated total bilirubin 2.8 (direct 0.7/indirect 2.1). Patient was managed as a case of fever with thrombocytopenia and minimal hepatic dysfunction. Chest and abdominal radiographs revealed no specific abnormalities but an ultrasound scan of the abdomen showed a hepatosplenomegaly with heterogeneous splenic parenchyma.

Inspite of adequate supportive care, patient was complaining of persistent pain in the left hypochondrium with tenderness and there were occasional spikes of fever. IgM testing for

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Received: 16.05.2016; Accepted: 04.04.2019
Dengue, Leptospirosis, Scrub typhus, Brucella and Rapid Malarial Test to look for infectious process all turned out negative. Echocardiography was normal and blood and urine cultures were negative for specific pathogens. Platelet function studies were found to be within normal limits.

In view of the persisting abdominal symptoms, a CT scan of the abdomen and pelvis was ordered with IV contrast which demonstrated moderate splenomegaly, with findings compatible with contained splenic rupture predominantly involving the superior and anterior aspect with minimal subcapsular/perisplenic hematoma (Figure 1). Since there was no history of trauma, Monospot and Epstein-Barr virus panels were added to rule out possible infectious process. Monospot was negative and Epstein-Barr virus (IGG, IGM) panel demonstrated EBV VCA IGG negative, EBV VCA IGM positive, and EBV NUCLEAR AG, IGG negative.

Being a contained rupture and since patient was haemodynamically stable, after consulting with radiology and surgical departments, it was decided to treat the patient conservatively and to repeat CT scan of abdomen after 8 weeks. Patient improved symptomatically within a few weeks and was discharged with the advice to refrain from severe physical exertion for 4 weeks.

Repeat imaging (Figure 2) done after 8 weeks showed findings suggestive of a resolving splenic laceration/hematoma with size of spleen, heterogeneity of splenic parenchyma and perisplenic hematoma reduced in size compared to the previous scan.

**Discussion**

Infectious Mononucleosis is a clinical syndrome caused by Epstein-Barr virus (EBV) that is particularly common in adolescents and children. Typical features of Infectious Mononucleosis include fever, pharyngitis, posterior cervical lymphadenopathy, headache, nausea vomiting and anorexia.³

Potentially serious complications from Infectious Mononucleosis include Acute interstitial nephritis, Hemolytic anemia, Myocarditis and cardiac conduction abnormalities, neurologic abnormalities, cranial nerve palsies, encephalitis, meningitis, mononeuropathies, retrobulbar neuritis, thrombocytopenia, upper airway obstruction, splenomegaly and splenic rupture.² An important feature of Infectious Mononucleosis is the proliferation of mononuclear cells especially in the lymphoid tissue leading to splenomegaly which is usually reversible and thinning of splenic capsule which may lead to potentially fatal complication of splenic rupture.³ Splenic rupture occurs in about 0.1% of the cases and its presentation may vary from persisting right upper quadrant pain of abdomen or Kehr’s sign, which presents as left shoulder pain from the irritation of diaphragmatic nerves caused by the presence of hemoperitoneum or patient could even be in shock due to acute blood loss.³ A high index of suspicion is always warranted in cases of Infectious Mononucleosis with such a clinical profile to reach at a diagnosis of splenic rupture. Even though there has been a few case reports of spontaneous splenic rupture after Infectious Mononucleosis in world literature, such reports from India are quite rare and hence the importance of our case.

In our case, even though there was no appreciable hepatosplenomegaly clinically, an emergency ultrasound scan of the abdomen revealed a hepatosplenomegaly with heterogeneous splenic parenchyma. In view of persisting abdominal

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**Table 1: AAST splenic injury scale (1994 revision)**

<table>
<thead>
<tr>
<th>Grade*</th>
<th>Type</th>
<th>Description of injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hematoma</td>
<td>Subcapsular, &lt;10% surface area</td>
</tr>
<tr>
<td>II</td>
<td>Laceration</td>
<td>Capsular tear, &lt;1 cm parenchymal depth</td>
</tr>
<tr>
<td>III</td>
<td>Hematoma</td>
<td>Subcapsular, 10%-50% surface area; intraparenchymal, &lt;5 cm in diameter</td>
</tr>
<tr>
<td>IV</td>
<td>Laceration</td>
<td>1-3 cm parenchymal depth that does not involve a trabecular vessel</td>
</tr>
<tr>
<td>V</td>
<td>Laceration</td>
<td>&gt;3 cm parenchymal depth or involving trabecular vessels</td>
</tr>
<tr>
<td></td>
<td>Laceration involving segmental or hilar vessels producing major devascularization (&gt;25% of spleen)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Laceration</td>
<td>Completely shattered spleen</td>
</tr>
<tr>
<td></td>
<td>Vascular</td>
<td>Hilar vascular injury with devascularizes spleen</td>
</tr>
</tbody>
</table>

Note: AAST=American Association for the Surgery of Trauma. From reference 34. Advance one grade for multiple injuries up to grade III; Source: http://www.aast.org/library/traumatools/injuryscoringscales.aspx#spleen
Symptoms, we suspected a splenic rupture and proceeded with a contrast enhanced CT scan of the abdomen which is the recommended imaging modality of choice in suspected splenic injuries in hemodynamically stable patients. According to American Association for the Surgery of Trauma, splenic injury is graded as per the findings of the contrast enhanced CT scan.

Contrast enhanced CT findings may include splenomegaly, hemoperitoneum, lacerations, subcapsular/intraparenchymal hematomas and pseudo aneurysms/AV fistulas. Lacerations appear as linear or branching hypodensities [6]. Subcapsular hematomas can be seen as low-density fluid adjacent to the spleen that distorts the splenic architecture. Parenchymal hematoma appears as a focal hypodense area within the enhanced splenic parenchyma with an intact capsule. Active hemorrhage appears as a high-density (80-95HU) material due to the extravasation of contrast media that increases in size on delayed imaging. Pseudo aneurysms and AV fistulas have a similar appearance to active hemorrhage on initial scanning but do not increase in size on delayed phases.[5,6] Haemoperitoneum can be accurately detected on a CT scan when a patient is in the supine position, blood from the splenic injury passes via the phrenicocolic ligament to the left paracolic gutter and the pelvis.

Ever since spontaneous splenic rupture secondary to Infectious Mononucleosis was first reported in the literature by King in 1941, a very alarmingly high mortality rate of approximately 30 percent wars reported and although this mortality rate was based on only a few cases, it led physicians to view splenectomy as the treatment of choice for the disease. Due to the overwhelming risk of post splenectomy infection, there has been a shift away from operative treatment of splenic injury. Non-operative management has become the standard of care in hemodynamically stable patients. The standard criteria for non operative management are: (a) hemodynamic stability (b) no rebound tenderness and guarding (c) blood transfusion requirement ≤ 4 units (d) no impairment of consciousness (e) age < 55 years and (f) radiologically documented splenic injury.

These are not always rigid constraints and the only absolute indication for emergency laparotomy is hemodynamic instability. But in majority of the cases, conservative non-operative management with preservation of spleen should be the aim unless the patient is haemodynamically unstable or when there is failure of conservative management. The advantages of non-operative management are that it eliminates the risk of postsplenectomy sepsis and saves the patient from potential perioperative complications. However, non-operative management is not without risk. The patient may be prone to delayed splenic rupture and as a result, may require a longer period of follow-up with slower return to normal activities. Splenic angiography and arterial embolization may be attempted wherever the facilities are available if the grade of injury is amenable to it. At the time of discharge patient should also be instructed to avoid strenuous physical activities and contact sports until the injury has resolved. Considering the limited sensitivity of physical examination for the detection of splenomegaly, it would be ideal to obtain an ultrasound examination in the high-risk athlete before return to play to assure a return to normal size spleen.

Conclusion

Spontaneous splenic rupture is a rare and life-threatening complication if not promptly recognized and treated which occurs in about 0.1-0.5% of the cases. Its presentation may vary from persisting mild abdominal pain to even hypovolema and shock in fatal cases. As demonstrated in this case, it is therefore prudent that healthcare providers remain vigilant for potential complications of EBV especially when there are atypical symptoms/signs or when the patient’s presenting complaint and subjective findings markedly differ from the objective findings noted on physical examination. A high index of suspicion is always warranted in cases of INFECTIOUS MONONUCLEOSIS with such a clinical profile to reach at a diagnosis of splenic rupture. Even though there has been a few case reports of spontaneous splenic rupture after Infectious Mononucleosis in world literature, such reports from India are quite rare and hence the importance of our case. Surgical management used to be the prime modality of treatment previously, but there has been a shift away from operative treatment of splenic injury and non-operative management has become the standard of care in hemodynamically stable patients. Patients diagnosed with IM should be advised to seek medical care immediately if abdominal pain develops. At the time of discharge all patients should be advised to refrain from physical activity for at least 4 weeks, even if asymptomatic and strong consideration should be given to imaging to confirm that the abnormal spleen has returned to a normal size.

References


Arbekacin - A Novel Antibiotic for Critical Infections

Gajanan Panchal¹, Rahul Pandit², Abhijit Trailokya³, Akhilesh Sharma⁴

Abstract
Antibiotic resistance is one of the biggest menace to global health. Deaths from Drug-resistant infections is set to escalate exponentially. Pipeline for new antibacterials is almost empty. The World Health Organization has reinforced its warning that to tackle growing threat of antimicrobial resistance, development of a new antibiotics is seriously lacking. Arbekacin is a novel aminoglycoside primarily used in the treatment of infections caused by resistant Staphylococcus Aureus i.e. Methicillin Resistant Staphylococcus Aureus (MRSA). Besides MRSA it also demonstrates activity against Enterococci and several Gram negative pathogens such as Klebsiella pneumonia, Pseudomonas aeruginosa, Acinetobacter baumannii including resistant strain. Arbekacin which has been used in Japan and Korea since more than two and half decades has been recently approved in India. This review will examine how Arbekacin evades the common mechanisms of antibiotic resistance, the pharmacokinetics of Arbekacin, and the various pharmacological properties and its spectrum of in vitro activity. The results of clinical trials on Arbekacin are also described, as is the patient safety and tolerability observed during these studies.

Introduction
Bacterial infections are one of common afflictions seen in health care. These infections are frequently acquired by critically ill patients in hospital settings with intensive/critical care units (ICU/CCU) being the hub of infection causing bugs.¹ Staphylococcus aureus is a major bacterial human pathogen that causes a wide variety of clinical manifestations.² Further, emergence of its drug-resistant strain i.e., methicillin resistant S. aureus (MRSA) is a major health concern globally in hospitalized patients and community settings.³ It imposes a serious healthcare burden with significantly increased morbidity and mortality. Apart from S. aureus and its resistant strain i.e., MRSA, Gram-negative bugs representing common nosocomial isolates including Pseudomonas aeruginosa, Acinetobacter spp., Escherichia coli and Klebsiella sp. are major concerns in India.¹ These may cause infections ranging from urinary tract infections (UTI) to pneumonia or other complicated blood stream infections. There has been a widespread high prevalence of Gram-negative infections in hospital settings.⁴ Moreover, emergence of their multidrug resistant (MDR) strains, also called as superbugs further adds on to the complexity of situation, rendering them difficult to treat.¹

Currently available and commonly used anti-MRSA drugs in India include Vancomycin, Teicoplanin, Linezolid, Daptomycin. Recently there are reports of Vancomycin treatment failure rates associated with an increase in the minimum inhibitory concentration as well as a decrease in the rate of bacterial killing. The constitutive limitations of vancomycin include poor tissue penetration, especially in the lung, relatively slow bacterial killing and the potential for toxicity. In addition, intermediate-level vancomycin resistance has emerged among staphylococci, with some cases of fully resistant strains.⁵ Although the other drugs do have certain differentiating attributes and may offer some advantages over vancomycin, they also have significant limitations. Teicoplanin is a glycopeptides with slow bactericidal activity and a spectrum of activity and efficacy comparable to vancomycin.⁶ Heterogeneous resistance to vancomycin and teicoplanin among Staphylococcus spp. has been reported.⁷ In the scenario of the emergence and spread of resistance to Vancomycin as well as other glycopeptide agents like teicoplanin among clinically
Staphylococcus aureus
Methicillin-resistant
been approved by DCGI in 2017.
Further, it is known to be associated
and coagulase-negative staphylococci
important gram-positive cocci
like Enterococcus species, S. aureus,
and coagulase-negative staphylococci
it becomes difficult to manage serious infections caused by such pathogens. The major concern with daptomycin use is that it cannot be administered in patients with lower respiratory tract pneumonia. It is destroyed by pulmonary surfactants and hence, can’t be used in pneumonia. Further, it is known to be associated with eosiinophilic pneumonitis and rhabdomyolysis. The ease of oral administration of linezolid can be easily exploited in clinical practice, especially its use in treating MRSA in a community setting.

Introduction to Arbekacin (1-N-(S)-4-amino-2-hydroxybutyl dibekacin) and its Unique Chemical Structure

The drug Arbekacin was developed in Japan and has been licensed for use under trade name “Habekacin” for treatment of MRSA caused sepsis and pneumonia since 1990. Other than Japan, it is available in Korea for the same indication since year 2000 and laks of patients have been treated safely using this drug. Arbekacin has been approved by DCGI in 2017.

Arbekacin: chemical structure

Arbekacin, a derivative of aminoglycoside dideoxykanamycin B (dibekacin) belonging to kanamycin family. Arbekacin has the structure of 1-N-[(S)-4-amino-2-hydroxybutyryl (AHB)-DKB. Due to the introduction of AHB to 1-N position of DKB, the resulting Arbekacin exhibited activity against DKB-resistant bacteria.

Arbekacin is stable to the aminoglycoside-inactivating enzymes produced by MRSA, such as aminoglycoside-phospho transferase (APH), aminoglycoside-adenyltransferase (AAD), and aminoglycoside-acetyltransferase (AAC). Gentamycin, Amikacin, Tobramycin, and kanamycin were completely inactivated by APH (2\(^\circ\)). However, Arbekacin still showed about 50% activity against APH (2\(^\circ\)). Furthermore, Arbekacin was not inactivated by AAD (4\(^\circ\)) and APH (3\(^\circ\)), and also showed stability to these enzymes.

Mechanism of action

It damages microbial cell membrane and binds both the ribosomal subunits i.e., 50S and 30S, thereby leads to codon misreading and thus inhibits translation.

Arbekacin: Spectrum of activity

Arbekacin has broad antimicrobial activities. Arbekacin shows good bactericidal activity against Gram-positive bacteria MRSA. It also shows antibacterial activities against high-level gentamicin-resistant Enterococci. Besides gram positive bacteria, it also shows activity against Gram-negative bacteria including multi-drug-resistant Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae.

Bactericidal effect of Arbekacin against MRSA

Arbekacin also shows concentration-dependent bactericidal activity. Viable counts of MRSA were rapidly decreased in a short period after the addition of Arbekacin in comparison with those of Vancomycin (VCM), Teicoplanin (TEIC), and Linezolid (LZD).

Post-antibiotic effect of Arbekacin

Post antibiotic effect is another characteristic of aminoglycoside antibiotics. When the antibacterial activity of arbekacin was compared with that of vancomycin, Arbekacin showed concentration-dependent bactericidal activity against MRSA strain 1936 (0.5-2 x MIC), but vancomycin showed only slight bactericidal activity, even at high concentrations of 19 x MIC. Arbekacin demonstrated a longer post-antibiotic effect (2.3-3.8 hours) than vancomycin (0-1.3 hours) against MRSA strain 1936. Arbekacin induced marked morphological changes at 0.5 x MIC and the changes remained for 2 h after removal of the agent. When exposed to 0.5 x MIC of vancomycin, no notable morphological change was observed in the treated cells.

Biofilm penetration by Arbekacin

A Biofilms are a major concern for clinicians in the treatment of infectious disease because of their resistance to a wide range of antibiotics. Morphological studies using scanning electron microscopy and histochemical staining demonstrated that an Arbekacin induced dramatic changes in the biofilm membranous
Inhibition of toxic shock syndrome toxin-1 (TSST-1) by Arbekacin

The effect of Arbekacin, Vancomycin, and Teicoplanin on the production of TSST-1 by MRSA strains has been reported. In logarithmic infections phase cultures, Arbekacin, Vancomycin, and Teicoplanin inhibited TSST-1 production by 85%, 10%, and 25%, respectively, at the concentration of one fourth of each MIC.\(^{11}\)

Arbekacin in Treatment of MRSA: Indian Data

A phase III, multi-centric, open-label, randomized clinical trial was conducted on a total of 162 Indian patients with MRSA infections (Pneumonia, SSTI viz. post-operative wounds, infected ulcers, and deep abscess). The patients received arbekacin and 127 had teicoplanin and analysis was performed on 71 patients form each group.

Table 2: Clinical evidence of Arbekacin against MRSA

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Study Population and Study detail</th>
<th>Results / Main outcome / Comment</th>
</tr>
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<tbody>
<tr>
<td>Hwang 2013(^{10})</td>
<td>Arbekacin and vancomycin</td>
<td>146 patients having MRSA infections (Sepsis, wound- and catheter-related infections, other MRSA infections)</td>
<td>Efficacy: Bacteriological efficacy response: 71.2% by arbekacin and 79.5% of vancomycin Clinical efficacy response: 65.3% by arbekacin and 76.1% by vancomycin Safety: Arbekacin had better safety profile than vancomycin Significantly higher ADRs in vancomycin (32.9%) group compared to arbekacin (15.1%) (p=0.039) Reported ADRs: Nephrotoxicity, leukopenia, hepatotoxicity, skin rash and drug fever</td>
</tr>
<tr>
<td>Ueno 2012(^{17})</td>
<td>Irrigation using arbekacin for 6 to 46 days</td>
<td>Six patients having MRSA empyema after lung resection due to primary and metastatic lung cancer of lung donation for transplant</td>
<td>Efficacy: Thoracic cavity irrigation using arbekacin was suggested to be readily available effective and safe method for treatment of MRSA empyema after lung resection Safety: No arbekacin induced nephrotoxicity or any other complications were seen Bacterial resistance to arbekacin was not detected in thoracic cavity of any patient</td>
</tr>
<tr>
<td>Matsumoto 2013(^{18})</td>
<td>Arbekacin</td>
<td>89 patients having pneumonia or sepsis due to MRSA were enrolled with efficacy analysis being performed on 29 patients</td>
<td>Efficacy: 95% Efficacy rate (19/20 patients) was found at doses of 5–6 mg/kg or higher with rate of 87.5 % efficacy (7/8) for MRSA sepsis and 90.5 % efficacy (19/21) for MRSA pneumonia Overall efficacy rate was 89.7 % (20/22) Safety: Incidence rate of arbekacin related ADRs was only 17.2 % (ADR: elevated AST and ALT, liver disorder, decreased platelet count, renal disorder and constipation) Thus, for achieving high efficacy and low ADR incidence, the study recommended setting of initial arbekacin dose 5–6 mg/kg or higher and should be adjusted to achieve C(<em>{\text{peak}}) ≥10–15 µg/ml and C(</em>{\text{trough}})&lt;2 µg/ml</td>
</tr>
<tr>
<td>Hwang 2013(^{19})</td>
<td>Arbekacin and Vancomycin for at least 4 days</td>
<td>122 patients with MRSA SSTI (63 in arbekacin, 59 in vancomycin group)</td>
<td>Efficacy: Bacteriological efficacy response: Arbekacin had 73.0% (46/63) efficacy with 60.3–83.4% of CI while vancomycin had 83.1% (49/59) with 71.0 to 91.6% of CI (p=0.264); Clinical efficacy response: Arbekacin had 67.2% (41/61) efficacy with 52.0 to 76.7% of CI while vancomycin had 78.0% (46/59) efficacy with 65.3 to 87.7% CI (p=0.265) Safety: Complication rate was found to be significantly higher in vancomycin group (49.2%; CI 35.9 to 62.5%) than arbekacin (15.9%; CI 8.4 to 29.0%) (p=0.001); ADRs reported in study were nephrotoxicity, leukopenia, hepatotoxicity, skin rash and drug fever Thus, arbekacin could be a reasonable substitute for vancomycin and can be used as a primary antibiotic for treating MRSA SSTIs</td>
</tr>
<tr>
<td>Hwang 2015(^{20})</td>
<td>Arbekacin and Vancomycin</td>
<td>95 patients diagnosed with chronic suppurative otitis media, of which, 20 were treated with arbekacin and 36 with vancomycin</td>
<td>Efficacy: Bacteriological efficacy: 85.0% with arbekacin and 97.2% with vancomycin Clinical efficacy: 90.0% with arbekacin and 97.2% with vancomycin No significant different was observed between the two Safety: Complication rate was significantly higher in vancomycin group (33.3%) than in the arbekacin group (5.0%) (p=0.020); ADR observed in vancomycin group were hepatotoxicity, nephrotoxicity, leukopenia, skin rash, and drug fever Arbekacin was therefore suggested to be a good alternative drug to vancomycin for treating chronic suppurative otitis media patients</td>
</tr>
<tr>
<td>Hwang 2016(^{21})</td>
<td>Arbekacin or Teicoplanin</td>
<td>235 patients having MRSA infections (SSTI, pneumonia, otitis media, sepsis and other); 108 received arbekacin and 127 had teicoplanin and analysis was performed on 71 patients form each group</td>
<td>Efficacy: Bacteriological efficacy of the arbekacin was slightly higher than teicoplanin (72.9% for arbekacin and 70.3% for teicoplanin), but difference between two was statistically non-significant (p=0.835); Clinical efficacy of the arbekacin group (59.4%) was lower than that of the teicoplanin group (69.1%), however, difference was statistically nonsignificant (p=0.257); Safety: Complications were significantly higher in teicoplanin group (36.6%) than in the arbekacin group (18.3%) (p=0.003); Complications observed were nephrotoxicity, leukopenia, hepato-toxicity, skin rash, drug fever, and gastrointestinal problems. Arbekacin was suggested to be a good alternative drug to teicoplanin or vancomycin for treatment of MRSA infection.</td>
</tr>
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</table>

Arbekacin was suggested to be a good alternative drug to teicoplanin or vancomycin for treatment of MRSA infections (Pneumonia, SSTI viz. post-operative wounds, infected ulcers, and deep abscess). The patients structure as well as in the inflammatory response, resulting in eradication of the biofilm structure and resolution of inflammation.\(^{13}\)

The effect of Arbekacin, Vancomycin, and Teicoplanin on the production of TSST-1 by MRSA strains has been reported. In logarithmic infections phase cultures, Arbekacin, Vancomycin, and Teicoplanin inhibited TSST-1 production by 85%, 10%, and 25%, respectively, at the concentration of one fourth of each MIC.\(^{11}\)
vancomycin in the management of MRSA infections. 

Arbekacin was also the most potent aminoglycosides tested against carbapenemase producing K. pneumonia. 

- Arbekacin and gentamycin were the most potent aminoglycosides tested against ESBL-producing A. baumannii. 
- The MIC\textsubscript{\text{90}} of arbekacin for E. coli was 2-4-fold lower than that of amikacin and gentamicin, respectively. 
- Arbekacin was 2-, 4-, and 16-fold more potent than amikacin, gentamycin, and tobramycin against extended-spectrum \( \beta \)-lactamase (ESBL)-producing E. coli, respectively. 
- Arbekacin and amikacin were the most potent aminoglycosides tested against ESBL-producing K. pneumonia. 

Activity Against Gram Negative Pathogens

- Arbekacin was also the most potent aminoglycosides tested against imipenem-resistant A. baumannii. 
- The MIC\textsubscript{\text{90}} of arbekacin for E. coli was 2-4-fold lower than that of amikacin and gentamicin, respectively. 
- Arbekacin was 2-, 4-, and 16-fold more potent than amikacin, gentamycin, and tobramycin against extended-spectrum \( \beta \)-lactamase (ESBL)-producing E. coli, respectively. 
- Arbekacin and amikacin were the most potent aminoglycosides tested against ESBL-producing K. pneumonia. 

Arbekacin in combination with other antibiotics

- A combination of aztreonam and arbekacin was effective for treating a patient with acute myelogenous leukemia with multidrug-resistant P. aeruginosa bacteremia. 
- In a study by Lee et al., arbekacin with vancomycin, teicoplanin, or ampicillin-sulbactam showed \textit{in vitro} synergistic interaction against hetero-VISA and MRSA strains. 
- Assessment of \textit{in vitro} MIC of arbekacin against 200 Acinetobacter baumannii-calcoacetics isolates recovered from wounded soldiers showed that 97.5% of the isolates had Arbekacin MICs <8 mg/mL and 86.5% had MICs <4 mg/mL. In addition, it was reported that the antibacterial effect was enhanced with arbekacin-carbapenem combinations. 

Administration of arbekacin: Once-daily versus divided dose

Phase I clinical studies and Experimental studies were conducted for the assessment of the efficacy and safety of once-daily administration of Arbekacin. No significant difference was found between once-daily and divided administration regimens in protection against an experimental MRSA infection in mice. In the phase I clinical study of 5-day repeated administration of 200 mg/day of arbekacin, headache and increase in WBC sediment in the urine was noted in 1 volunteer; however, these were not confirmed to be attributable to Arbekacin. No abnormal laboratory test results were obtained other than increases in beta 2-microglobulin, NAG and gamma-GTP levels, each of which returned to normal after the completion of Arbekacin administration. No abnormality was observed in the audiometry examination. 

Arbekacin: Drug profile

- Composition: Each 4 ml of Arbekacin ampoule contains Arbekacin sulfate equivalent to Arbekacin 200 mg
- Indication: Treatment of pneumonia and sepsis caused by MRSA
- Dosage & Administration: Adults: 150 – 200 mg/day as single dose IV drip for 30 min – 2 hours
- Method of administration: It should be mixed with 0.9% sodium chloride & administered by intravenous infusion over period of 30 minutes to 2 hrs.
- Pharmacokinetics of Arbekacin

Pharmacokinetics After Single Administration of 200 mg

- Serum half-life (T1/2) ~ 2.30 hours
- Urinary recovery rate (0-48 hours) ~ 86.75%
- No significant differences between day 1 & day 5 in a 5-day repeated administration study
- In patients receiving 200 mg of Arbekacin once daily, mean Cmax and Ctrough values were 16.2 \( \mu \) g/mL and 1.1 \( \mu \) g/mL, respectively, and the elimination half-life was prolonged in patients with moderate to severe renal dysfunction.
- Pharmacokinetics in children: Recommended dosing regimens were 5 mg/kg every 48 hours for preterm infants with postnatal age <28 days, 5 mg/kg every 24 hours for preterm infants with postnatal age ≥28 days, and for term infants 4 mg/kg every 24 hours. These initial dosing regimens could manage the maximum concentration (Cmax) 7–15 \( \mu \) g/mL and trough concentration (C\text{trough}) 0–2 \( \mu \) g/mL in 72.2%–93.5% of infant patients.
- Therapeutic drug monitoring
Use of Arbekacin in patient with renal inadequacy: “Interval extension” method may be used by cutting in half of maintenance dose and using same priming dose like patient having a normal renal function.29

For e.g. Priming dose: 75-100 mg; Maintenance dose: half of priming dose

Dosage interval: based on creatinine clearance.29

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dosage interval</th>
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<tr>
<td>20-25 ml/min</td>
<td>12-24 hours</td>
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<tr>
<td>≤ 20 ml/min</td>
<td>24-48 hours</td>
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Nephrotoxicity and ototoxicity

It has been found that at a high total dose of over 5,000 mg, there could be nephrotoxicity with Arbekacin whereas the risk of nephrotoxicity is less at a total dose of less than 5,000 mg.30 In an experimental study by Nizato T et al. 1994, Arbekacin was found less toxic to kidney than Vancomycin.30

It is supposed that ototoxicity of aminoglycoside occurs because of the gradual drug accumulation in endolymph and perilymph in the inner ear. In an experimental study by Kurebe, M et al. 1986 Arbekacin was found to be less ototoxic than Amikacin.31

Summary and conclusions

Arbekacin - a novel aminoglycoside antibiotic is stable to pathogens that produce aminoglycoside-inactivating enzymes. Arbekacin exhibits more potent antimicrobial activity compared to other anti-MRSA antibiotics such as linezolid, vancomycin, and teicoplanin. Pharmacokinetic advantages of arbekacin such as concentration-dependent bactericidal activity and prolonged post-antibiotic effect are more appreciable. Hence, the viable counts of MRSA rapidly decline in a short period. Arbekacin inhibits toxic shock syndrome more effectively than other antibiotics such as teicoplanin and vancomycin. Arbekacin exhibits good activity against Gram negative bacteria including multdrug-resistant strains such as P. aeruginosa, carbapenemase-producing K. pneumoniae, ESBL-producing K. pneumoniae, ESBL-producing E. coli and A. baumannii because of its synergistic effect in combination with beta-lactams including carbapenems. In a recent clinical study in Indian patients, arbekacin has shown comparable efficacy with vancomycin for treatment of MRSA infections in terms of clinical cure and microbiological cure rates; however, there was faster resolution of fever with arbekacin as compared to vancomycin, which is an indicator of efficacy of arbekacin in speedy restoration of afebrile status in patients with MRSA infection. Thus, arbekacin is turning out to be an alternative to current anti-MRSA drugs for the treatment of MRSA infections which additionally exhibits activity against various Gram negative bacilli.

References

John Enders-Pioneer Virologist

Jayant Pai-Dhungat

John Franklin Enders (1897-1985) was born in Hartford, Connecticut. After his initial education and graduation at Yale, he studied at Harvard, choosing a PhD in microbiology over medicine. He set up a Research Division of Infectious Diseases at Children’s Hospital of Boston (Harvard), where.

At Harvard, Enders worked on bacteriology and immunology, and was also a member of teaching staff. He first studied the elucidation of certain factors related to bacterial virulence and resistance of the host organism (1930s). In 1938, He began the study of some mammalian viruses, and in 1941, undertook study of mumps virus with his colleagues. This work provided serological tests for diagnosis of mumps.

In 1946, Enders was asked to establish a laboratory for research in infectious diseases at the Children’s Medical Center, Boston. Here he was joined by Frederick Robbins (1916-2003) and Thomas Weller (1915-2008). Enders sought ways to perfect technique of tissue culture to grow polio virus in test tube. This was tried earlier with limited success; in that, there was failure of polio virus growth in extra neural tissue. Weller and Enders used a mixture of human embryonic (stillborn) skin and muscle tissue from the extremities. It was a suspended cell culture prepared by Weller for varicella (chicken pox) virus and was considered free from intact nerve cells. Enders made use of antibiotics discoveries; adding antibiotics to the media, he allowed the viruses to grow alone, devoid of contaminants. This procedure was very successful for growing polio virus. It became a major advance in the technique, making it possible not only for poliomyelitis virus, but also other viruses like measles, German measles, mumps, and chicken pox.

Weller and Robbins differentiated viruses by examining cells grown in test tubes with light microscope. They recognized that viruses injured cells in specific manner. By studying the pattern of such cell injury, they could distinguish one virus from other. For example, polio virus killed the cell in a distinctive pattern while measles virus enlarged the cells, forming many nuclei. In 1949, the paper by Enders, Weller, and Robbins which appeared in Science, describing the growth of polio viruses in non neural embryonic tissue, is now considered a land mark in virological research. These discoveries opened up a new approach to the study of viruses, for development of vaccines against polio and other childhood scourges. Weller and Robbins received credit for rubella vaccine. It also paved the way for fight against cancer and for studies in genetics.

John Enders was awarded 1954 Nobel Prize in physiology or medicine for cultivating poliomyelitis virus in non-nervous tissue culture with his younger colleagues and students, Frederick Robbins and Thomas Weller. Work was done during 1948-50

Simple and quiet man, Enders was known as a “modest chief”. He trained several generations of leading experts in infectious diseases. There are few scientists who would see to it that their younger colleagues share the recognition. Enders continued to work at Harvard and his laboratory until he was 80. He died in 1985 at the age of 88.
Study of Clinico-hematological Correlation in Cases of Glucose-6-Phosphate Dehydrogenase Estimation in a Tertiary Care Hospital

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1Addtnl. Prof., 2Asst. Prof., 3Ex-Postgraduate, BYL Nair Ch Hospital & TNMC, Mumbai, Maharashtra

Sir,

G6PD deficiency inherited as X linked recessive disorder is a significant health problem with 7.5% of world population having one or two genes for G6PD deficiency. In India with a diverse population, prevalence of G6PD deficiency is 0-10%. G6PD testing is done as a diagnostic test by standard quantitative spectrophotometric assay and qualitative NADPH fluorescence test.1

The present study included retrospective and prospective data from Department of pathology over a period of three years from August 2012-2015. Aim was to analyse and highlight the incidence of G6PD deficiency among various age groups of urban population visiting our tertiary care hospital. The study included quantitative estimation of G6PD and correlating with indications and haematological parameters. A total of 2115 blood samples were received during the three years period.

Complete clinical details were obtained from requisition forms or Medical Records. G6PD estimation was done by quantitative method based on Nicotinamide adenine dinucleotide phosphate (NADP) reduction on a semi-automated biochemical analyser of ERBA instruments. The normal reference of G-6-PDH in this study at 30 degree Celsius used was 4.6-13.5 U/g of Hb. Samples were labelled as G6PD normal or deficient. Statistical analysis was carried out using Chi Square test.

Out of a total 2115 samples tested, largest age group was less than 1years (29.9%) followed by 21-30years (24.6%) with male: female being 1.73:1 which was significant (p=0.04). Ethnicity wise distribution was not significant (p=0.21). Commonest clinical complaints were fever and chills (50.5%) followed by features of jaundice and lethargy in neonates (29.8%).

Commonest indication for G6PD was malaria (50.5%) followed by neonatal hyperbilirubinemia (29.8%) and dermatological disorders (14.7%). Out of 2115 cases, 62(3.2%) cases were G6PD deficient in 1934 valid samples. There was an increased incidence of males among deficient individuals. Majority of the diagnosed G6PD deficient cases in valid samples had malaria (93.6%) as the commonest indication followed by haemolytic anaemia and hyperbilirubinemia. On correlating with hemogram, statistically significant parameters such as hemoglobin and RBC indices among G6PD deficient individuals were observed.

In the present study, patient’s age variation, male preponderance and major presenting clinical complaints seen was well corroborated with Al Mendalawi et al, Issac et al and Tsegaye et al.1-3 About 151 samples (8.6%) showed invalid values due to inadequate volume < 2cc, lipemic samples and clotted samples. In this study, 49 (79%) of 62 G6PD deficient cases were significantly anemic (p value < 0.001) thus implying G6PD deficiency linked to haemolysis which was well corroborated with Al Mendalawi et al.1

In our study, low red blood indices and high reticulocyte count (1%-2.5%) were significant in G6PD deficient individuals (p<0.001) which was in concordance with Al Mendalawi et al.1 In present study, out of 1934 patients, 62 (3.2%) were found to be G6PD deficient unlike Issac et al reported a high 14.4% G6PD deficiency attributing to high prevalence of hemoglobinopathies and malarial parasitemia.2 The differences in the incidence of G6PD deficiency may be attributed to different genetic types of G6PD. In 3.2% (62cases) of the overall rate of G6PD deficiency, 93.5% cases were due to malarial parasitemia which corroborated with 90.9% observed by Tsegaye et al.3

To conclude, the present study highlights mandatory screening for G6PD deficiency detection in treatment of malaria and should be always included in malaria elimination programmes to ensure effective management. Also, G6PD screening should be considered in neonatal hyperbilirubinemia to avoid life threatening complications presenting later on in life.

References

Music Improves Immediate and Short-term Memory - A Preliminary Report

Murali Krishna K1, Anvesh Lanka2
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Sir,

Memory enhancement is a topic of interest that much sought after by both normal subjects and those with early dementia. Many studies have focused on using pharmacological agents to enhance memory. Music is a universal language. Recognition of familiar melodies is immediate and easy for many.1,2

This study was designed to observe weather music has any effect on potentiating memory in normal young individuals. Thus, the goals of the study were, to study the immediate and short-term memory of normal young adults after hearing to speech, evaluate the difference in immediate and short-term memory in young adults after hearing to a speech vs. hearing the same speech in the form of a song.

This was a case control observational study, conducted in GVP medical college conducted for 2 months. Subjects of the control group were subjected to listening to spoken lyrics in a song. Study group was subjected to listen to the same lyrics that the control group heard in the form of a song which was composed and sung. Both the groups were asked to reassembled separately after 3 days, and were asked to recollect and write the lyrics they heard, in the answer sheets supplied. Evaluation of the written papers was done and the number of sentences reproduced in the
same meaningful order was counted and marks were allotted accordingly.

On evaluation of test for immediate memory, control group scored a minimum of 1.5 and a maximum of 8 with a mean of 5.07. Study group scored a minimum of 3 and a maximum of 9 with a mean of 6.67. The p value between the groups is < 0.001. On evaluation of test for short-term memory, control group scored a minimum of 0.5 and a maximum of 7 with a mean of 3.37. Study group scored a minimum of 1 and a maximum of 9 with a mean of 5.26. The p value between the groups is < 0.001.

Our preliminary work presented here showed that music can enhance both immediate and short-term memory in normal young adults. Listening to speech in the form of a song containing music seems to enhance memory than listening to regular monotonous speech. In our study as we stimulated both the dominant, and non-dominant sensory cortex in the form of verbal and music for the study population. As Liégeois-Chauvel1 suggested that the non-dominant side being stimulated during music processing and as a known fact of the dominant sensory cortex being the one which processes the verbal information.

References


Association of Serum Prolactin with Troponin-I in Acute Myocardial Infarction

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Serum prolactin is elevated in acute myocardial infarction (AMI) and stroke. Prolactin’s causal role is suggested by its association with obesity, hypertension, diabetes, insulin resistance and dyslipidaemia. Hyperprolactinemia also leads to arteriosclerosis and impaired endothelial function.1 This study assessed serum prolactin in patients with AMI and evaluated its association with serum cardiac troponin – I.

An observational case control study was conducted in patients aged ≥ 18 years, diagnosed with Acute Myocardial Infarction (AMI) as per the Third Universal Definition by Thygesen K et al 2012, presenting in the ICCU. The conditions which alter serum prolactin levels were excluded.

91 patients of acute myocardial infarction participated in the study. All patients underwent routine investigations and cardiac troponin I and serum prolactin. The unpaired t-test and ANOVA were used for statistical analysis. The mean prolactin level was higher in females (21.47±4.24 ng/ml) than the males (19.70 ± 2.39 ng/ml, p=0.703) but statistically insignificant. The mean serum prolactin of AMI high prolactin group (n=57) was 10.42 ± 0.60 ng/ml and that of normal prolactin group (n=34) was 36.62 ± 4.20 ng/ml and that of normal prolactin group (n=57) was 10.42 ± 0.60 ng/ml. Mean serum troponin-I level was 11.61 ± 2.43 ng/ml in patients in high serum prolactin group as compared to 9.90 ± 1.28 ng/ml in patients in normal serum prolactin group but was not statistically significant (p=0.497). As shown in Figure 1 Serum prolactin did not correlate significantly with Troponin-I (p=0.622).

The prevalence of hyperprolactinemia is 0.4% (1 out of 250) in healthy adult population.3 In our study, 37.36% patients had high serum prolactin levels after an acute attack of myocardial infarction. The positive association between serum prolactin concentrations and myocardial infarction observed in our study is consistent with previous observations by Al-Kuraishy2 et al. This increase of systemic prolactin may be representative of the general neuroendocrine stress response, a role of prolactin as causal factor in the thrombotic diseases is possible also the increment in serum prolactin is positively correlated with troponin I which is unsimilar to our study and the differences could be due to assay used and time elapsed in getting Troponin I after AMI.

Mean serum prolactin was elevated in AMI patients. 37.36% of patients with AMI had high serum prolactin levels as compared to 4.44% thus showing the need to better understand role of Prolactin in Etiopathogenesis and Prognosis of Myocardial Infarction. However we could not find a significant association of Troponin-I levels with serum prolactin.

References

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<th>Selenium (40 mcg)</th>
<th>Lycopene (13 mg)</th>
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<tbody>
<tr>
<td>VIT B2 (60 mg)</td>
<td>VIT B6 (15 mg)</td>
<td>VIT B12 (35 mcg)</td>
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